Research Ethics Forum 2

Nuria Homedes
Antonio Ugalde *Editors*

Clinical Trials in Latin America: Where Ethics and Business Clash

Springer

Clinical Trials in Latin America: Where Ethics and Business Clash

RESEARCH ETHICS FORUM

For further volumes:
http://www.springer.com/series/10602

Nuria Homedes • Antonio Ugalde
Editors

Clinical Trials in Latin America: Where Ethics and Business Clash

Springer

Editors
Nuria Homedes
School of Public Health
Division of Management
Policy and Community Health
University of Texas Houston
Health Science Center
El Paso, TX, USA

Antonio Ugalde
Department of Sociology
University of Texas at Austin
Austin, TX, USA

This statement attests that Lugar Editorial S.A. of Argentina relinquishes at no cost all copyrights for the publication in English of **Ética y Ensayos Clínicos en América Latina** (English title: **Where Ethics and Business Clash: Clinical Trials in Latin America**) edited by Núria Homedes and Antonio Ugalde.

ISSN 2212-9529 ISSN 2212-9537 (electronic)
ISBN 978-3-319-01362-6 ISBN 978-3-319-01363-3 (eBook)
DOI 10.1007/978-3-319-01363-3
Springer Cham Heidelberg New York Dordrecht London

Library of Congress Control Number: 2013954711

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Foreword

This important, collaborative book describes current aspects of clinical research in Latin American countries from regulatory, operational, and cultural perspectives. The opportunity to write the introduction makes me very happy, for the following reasons:

- It allows me to continue to be a part of the story of countries that have been a very important part of my life, not only as a medical professional, but also – and perhaps most of all – in the field of human rights.
- It gives a direct opportunity to reflect systematically on a topic that has been very important throughout my many years of activity in clinical research: from the time when basic methodologies and strategies were first discussed to the present. I have seen the problems that Latin American countries have had to face to maintain autonomy and creativity in the context of a globalization that tries to make everyone accept and conform to supposedly perfect rules.
- I have been encouraged to reflect upon and compare what is happening in the health field and in the society of the European region where I have lived and worked for 30 years.

Based on actual experiences – some innovative – and on analysis and interpretation of regulatory frameworks, the authors of the different chapters have shared their thoughts, ideals, and concerns. This is how networks of researchers are built. It is the existence of these networks that allows researchers through the implementation of multinational or regional projects to test and promote the cultural and operational independence of many different players and leaders of clinical research, social epidemiology, the rational use of medications, and public health.

I must confess that the feelings of gratitude and honor when I accepted the invitation were gradually transformed when I read the contributions from the different countries. I doubted that I could add anything to such current descriptions and accurate analysis from the various authors, or to the observations that accompany the data in the profiles of the different countries. And so I chose to highlight points that, for me, personally, stood out in the notes I made as I read the various

chapters, and I have tried to express this book's contribution to the development of clinical research.

1. One of the most important and original features of this book is that in it we meet the people and hear the voices of the region, to see how they complement each other, and the potential – even more, the necessity – to find permanent ways that will allow networking. There is nothing original in forming work groups. In every sector of the health field we have a multitude of commissions, committees, and work groups, all created to design strategies, guidelines, agreements, etc. The originality of this book lies in stimulating participation by incorporating the voices of many different professionals who have less interest in seeking consensus than in starting a conversation – even some controversy – with the common objective of transforming clinical research into a pathway, a tool for exploration, and seeing to it that this takes place in a manner in which individual and collective human rights are respected. Both the participants, and the populations in which they live, must be subjects, not objects, of experimentation.
2. The International Conference on Harmonisation–Good Clinical Practice initiative (ICH-GCP), which during the past 20 years has been imposed mainly by market demand, has caused clinical trials to become one of the most important indicators of the conceptual, methodological, ethical, structural ambivalence that dominates the field of clinical research. Clinical trials have evolved in the medical context long before the harmonization initiative, to become the most incontestable method for answering, with greater certainty and responsibility and in a collegiate manner, a clinical therapeutic question using the logic of public health. The first clinical trial of "our" time coincides both chronologically and symbolically with the beginning of Great Britain's National Health Service. It transformed the problem of scarcity of a promising medication – streptomycin for the treatment of tuberculosis – into a randomized experiment to assure the scientific quality and robustness of the results, giving a concrete and objective answer to decision-makers (Editorial 1998).

   Medications (which are the almost exclusive focus of ICH-GCP) are only one component of a clinical trial; they are not the main actors. Clinical trials were born and are justified as exploration; based on clear concepts of clinical epidemiological, public health, patients' needs plausibility they sought to produce innovative responses to health problems lacking an answer. The clinical trial methodology was developed from this perspective, and by the end of the 1970s and through the beginning of the 1980s, almost all the methodological and statistical rules had been developed, and today are considered reference points. The so-called "population trials," large clinical trials which, during the later decades of the past century, have been the foundation of the great scientific advances in such pathologies as cancer, cardiovascular health, and AIDS, clearly come from this logic (Cochrane 1972; Silverman and William 1986; Peto et al., 1976; Yusuf et al. 1984; Bonati and Tognoni 1984; Tognoni and Bonati 1986; Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico 1986).

3. The progressive transformation of "health systems" into economic systems attractive to industrial interests that accelerated with the development of the World Trade Organization coincided with the transformation of clinical trials. In fact, the ICH-GCP grew in parallel with the report of the World Bank "Investing in Health," and the "Global Burden of Disease" project. These projects transformed diseases into points of reference and protagonists of the health systems, setting aside the real life of populations. In the same way, clinical trials became a tool to register and commercialize products to treat sickness. This apparently peaceful "revolution," presented in a language, which promised better protection for consumers and which standardized the control process through "ethics" committees, not be more profound. Medications are now the center and the objective of clinical trials and a strategy to produce industrial knowledge: individuals and populations are being permanently exposed to the risk of being converted into objects or tools (International Conference on Harmonisation 1996; The World Bank 1993; Murray et al. 1997).

   The dichotomy is perfect: clinical trials continue to be essential, and are "indicators" of the ability to find new answers to health problems. Their identity as tools to transform knowledge into marketable products makes them a critical part of the process. The multiplicity of "trials of products," seeking more differentiated participants in ever larger numbers coincides with the marginalization, possibly for economic reasons, of clinical trials that try to resolve the problems of a population. The "trials of products," which are the majority, impose their procedures and gradually become established as "rules or standards," not necessarily because they are superior methodologically, nor because they test hypotheses of greater clinical-epidemiological relevance, nor to give greater respect for the rights of the citizens and patients (Murray and Lopez 1997; Topol 2004; Angell 2000; Garattini and Chalmers 2009).

   In response to the demand of the markets, the regulatory agencies both globalize and multiply in each country. They adapt rapidly to new situations and become "experts in products" and guarantees that researchers and institutions comply with the procedures that the market requires. It is possibly the only way to survive economically, as it is this process that guarantees their budgets. Even communication – the personal communication between the physician and the patient – is transformed into a standardized process, "the module of informed consent," maximizing in this way the intrinsic dichotomy of the clinical trial of products (Henry 2006; Toussaint 2013; AIM et al. 2013; Tognoni and Geraci 1997; Hyder and Wali 2006).
4. The contributions to this book reflect the consequences of this dichotomy, which are also seen regularly in scientific journals. These stories appear on a daily basis, making specific references unnecessary here. It is the most dangerous trap for the development of a public health culture in the clinical trial sector. The comments I make below (desires, proposals, projects) are memory aids so that the current situation is not accepted as a reason to "protect oneself" from clinical trials; but exactly the opposite – to try to seriously examine the role of clinical trials as indicators of a health sector which always seeks to create knowledge, to answer real problems, and which respects the rights of participants.

4.1. The primary challenge and the first step in regaining intellectual autonomy (very critical for a sector that allows the "intellectual rights of products" to be converted into a sacrosanct absolute) is to recover the language, and the significance of words. It would seem that this is simple, but it is most important when regulations and standards for clinical trials are not only discussed, but are adopted and published. The appropriate nomenclature must be determined and used to adequately identify differing aspects: process *vs*. content; responsible sponsors and intellectuals *vs*. financiers; public ownership of information from patients and populations *vs*. the use of data to register and market products; personal communication with participants *vs*. standardized modules, which are examples of the lack of respect for the right to transparency in communication; the relevance of the hypothesis being evaluated by the simplest appropriate method *vs*. the bureaucracy of data collection, increasingly in the hands of non-independent entities such as the contract research organizations or CROs, which only serve to increase the costs of clinical trials.

4.2. A different language and way of thinking cannot begin, much less continue, if the players limit discussion and remain distant from each other. It is essential to accept a basic yet practical concept: clinical trials, and all that goes with them, derive their "legitimacy" from being an activity of clinical practice. The methods, rules, and tools of clinical trials are not (and should not be taught as being) something parallel, distinct, and difficult. In actuality, *they are an expression of responsible practice*, when physicians (or society) are challenged by ignorance and/or uncertainty about a problem (diagnostic, therapeutic or to improve the welfare of a patient or community) for which they have no adequate answer, and respond to the needs of, or rights to life and health for, individuals or populations.

4.3. We must become used to thinking (and speaking), including in this area, in ways that avoid confusion of the perspective of the formal-institutional majority with reality. From the methodological point of view, and not only from the human rights perspective, clinical trials for registering and marketing products are only a sub-group of different research strategies – and they are not the most important. It is their defenders – although numerically in the majority – who must justify and validate their legitimacy, and their attempts to impose "excessive" rules, instead of emphasizing basic quality criteria. It is these criteria which should be compulsory and an integral part of responsible clinical practice: they are the foundation from which to conduct clinical research, experimental or observational, with therapeutic, diagnostic, or physio-pathological goals.

4.4. To be translated into a perceptible and concrete culture, the legitimacy given to clinical research by constitutions and major international laws must be put into practice through field-based protocols and projects where a dialogue between clinical practice and research is established – because both are part of the same continuum. The challenge to focus projects and protocols to problems or populations – not occasionally, but as part of a

commitment and presence in society and in health systems – is at this time especially urgent in regions such as Latin America. It may not be easy, but there are examples in both general and specialized medicine showing what is possible. Economic problems, such as a lack of public investment and little promotion of "public health research" by international agencies, add to regulatory problems. Clinical trials are currently seen as a complex undertaking, representing additional and competing work in a health care practice. I want to emphasize this point, for the last time, for its negative consequences.

One of the contributions of this book is that it shows the pervasiveness of the problem, and it could be an important stimulus, from cultural and methodological perspectives (once more: these aspects are always complementary) to develop research protocols that are based on specific contexts. The clinical trials that a group of general physicians are thinking of conducting in Argentina on Chagas disease and strategies to control cardiovascular risks are examples of regional possibilities. There is no lack of ideas, but there is a lack of the confidence in having competence (which encompasses taking responsibility), *in the production of knowledge*, in response to the problems of patients, and without being primarily more or less compliant users of knowledge generated in contexts that prioritize the development of products (Hyder and Wali 2006; Tognoni et al. 2012).

4.5. The idea of actively reclaiming a perspective and language of autonomy must also apply to the construction and utilization of clinical trial registers. Promoting transparency regarding what is taking place (the reason for the existence of registers) is vital. Since registers in Latin America and the Caribbean are still in the stage of coordination-debate-development, I dare to make a wish that comes from my experience in the countries, regions, and international agencies that already have these registers.

The registers should not be limited to "register" to produce the maximum descriptive statistics of what is ongoing (how many trials, for what, in what sector, etc.). Perhaps I can explain what a register should be if I make a parallel with pharmaco-epidemiology: this discipline could be (and most often is) focused on describing "consumptions-prescriptions" of medications, but it should be more interested in the reasons for the prescription or the lack of access, and above all, their impact on the life and rights of the patients (Scurti et al., 2012). In the same way, a register-observatory, although quantitatively complete, is useful to know or "control" what happens, but above all to create material to promote an intensive dialogue between professionals and the public on the specific quality and the general direction of the "world of clinical trials." The country or regional registers can be transformed into tools of permanent education: a living "document in real time," which not only assists protocols to become publications, but, more importantly, is a source for monitoring and discussing the greater or lesser ability of the health system to express cultural autonomy in the search for answers to its most prioritized and relevant problems.

5. Two final wishes synthesize the consequences of the thoughts I have expressed for the "actors" at both extremes of the clinical trial theme: at one end, the regulatory agencies, and on the other, the communities of citizens.

   5.1. The national and international agencies, which create, adopt, and interpret rules and laws, may be considered as a perfect example of the dichotomy, which we have discussed, and which is one of the most important characteristics of the clinical trial research as it is being conducted, resulting in a divide between health and society. Maybe I am biased (in the most positive sense of the term) by having been a witness during 10 years (1998–2008) to what a regulatory agency could be and do (Agenzia Italiana del Farmaco or AIFA in Italy) when directed by a clear-thinking professional with a public health perspective – Dr. N. Martini. Under his direction, the interpretation of the essential role of the agency as controller was more effective (and less bureaucratic and rigid) because he was also actively promoting and supporting research. Two laws were approved; one to encourage and train general practitioners to take responsibility for problems within their sphere of practice, and the other to facilitate and reduce the cost of independent research related to population problems. The goal was to balance the quantitative dominance of "research to find products." These laws enabled active financing for public health research, and, in the area of continuing education, they gave more credit to those who interpret the duty of permanent education in terms of "producing new knowledge" than to those who attended "multimedia" conferences and listened to something that was already known or could be read anywhere (Ministero della Salute 2004; Filibeck et al. 2004; Editorial 2008).

   Agencies can exercise their role as "guarantor" from opposite perspectives:

   - As "negative" players, "against" the risks, or, from the "positive" position, by increasing the places and the opportunities for research by promoting research as a tool to expand the right to health
   - By representing a culture that believes that the growth of bureaucracy guarantees efficiency-transparency, or by stating that, by definition, the areas of competency of the agencies are those which require greater flexibility (beyond respecting the few essential rules) because, in research, clinical trials are a means of exploration which can be applied in many areas. Clinical trials require respect for the basic principles of the process, but their rigid application would violate another basic principle – respect for the "specificity" of people and populations.

   5.2. The citizens-patients – beyond what all the declarations "of principles" and of good-will say – in practice are absent and have no power (no matter their "symbolic" presence in Ethics Committees). Health continues to be, above all, in what is called the production of knowledge and in decision-making, the "property" of specialists. Admission into this club is strictly controlled, distinct criteria are used, and patients or citizens do not

participate directly, but only through their "representative(s)" (more and more often in the singular). The framework for my dream, which is consistent with the concept of clinical trials as a tool to change for the better the history of illnesses in populations, is found in epidemiology. More specifically, in the experiences called "community epidemiology" that developed precisely in Latin America. In this context, the community members are the producers and interpreters, responsible for the information, which describes them, and for the solutions to their problems, in a permanent conversation with but not dependent on a hierarchy of "specialists." This perspective is even more relevant for clinical trials that can be considered "legitimate," only when clinical promoters-actors and people with unanswered problems reciprocally recognize ignorance on both sides, seek an alternative, and decide together, to investigate a hypothesis for a solution, hoping that it will work. This is what we mean by the application of the basic principle of legitimacy-necessity of research-experimentation-clinical trial as an integral part of the practice of medicine (Cecomet 2010; Torres Goitia 2008; Breilh 2008).

As indicators of the ability of medicine to take responsibility for innovation and transparency, clinical trials can – perhaps must – be experiments of democracy. The challenge is the same, although the subjects will have different names and needs: patients *vs*. citizens, life *vs*. health. The respect for rights is an ongoing journey, always travelling on new paths: experiments, where responsibilities cannot be compartmentalized, because – in society and in health – the content and relationships of life are profoundly intertwined. It should be unimaginable that products could become the primary goal and end-point of clinical research.

Gianni Tognoni

References

AIM, ISDB, MiEF, and WEMOS. 2013. *Proposed regulation on clinical trials: Joint analysis*, 5 February. http://english.prescrire.org/en/79/207/46302/2507/2506/SubReportDetails.aspx. Accessed 23 Oct 2013.

Angell, M. 2000. The pharmaceutical industry – To whom is it accountable? *New England Journal of Medicine* 342(25): 1902–1904.

Bonati, M., and G. Tognoni. 1984. Has clinical pharmacology lost its way? *Lancet* 323(8376): 556–558.

Breilh, J. 2008. Latin American critical ('Social') epidemiology: new settings for an old dream. *International Journal of Epidemiology* 37(4): 745–750.

Cecomet. 2010. *Epidemiologìa Comunitaria: las periferias toman la palabra*. Ecuador: Cecomet.

Cochrane, A.L. 1972. *Effectiveness and efficiency. Random reflections on health services*. London: Nuffield Provincial Hospitals Trust.

Editorial. 1998. Fifty years of randomized controlled trials. *British Medical Journal* 317(7167). doi:10.1136/bmj.317.7167.0.

Editorial. 2008. Clean hands, please. *Nature* 454(7205): 667.
Filibeck, U., A. Addis, C. Tomino, and N. Martini. 2004. European clinical trials directive: The Italian position. *Lancet* 363(9421): 1651–1652.
Garattini, S., and I. Chalmers. 2009. Patients and the public deserve big changes in evaluation of drugs. *British Medical Journal* 338: b1025.
Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). 1986. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 327(8478): 397–402.
Henry, M.S. 2006. Uncertainty, responsibility, and the evolution of the physician/patient relationship. *Journal of Medical Ethics* 32(6): 321–323.
Hyder, A.A., and S.A. Wali. 2006. Informed consent and collaborative research: Perspectives from the developing world. *Developing World Bioethics* 6(1): 33–40.
International Conference on Harmonisation (ICH). 1996. *International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH harmonised tripartite guideline. Guideline for good clinical practice*. Geneva: ICH.
Ministero della Salute. 2004. Documento programmatico sulla sperimentazione clinica dei medicinali. *Bollettino d'Informazione sui Farmaci* 11(1):6–8. http://www.agenziafarmaco.gov.it/wscs_render_attachment_by_id/111.30602.1137602090158e343.pdf?id=111.30608.1137602090224. Accessed 23 Oct 2013.
Montalvo, G., F. Avanzini, M. Anselmi, et al. 2008. Diagnostic evaluation of people with hypertension in low income country: Cohort study of "essential" method of risk stratification. *British Medical Journal* 337: a1387.
Murray, C.J., and A.D. Lopez. 1997. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* 349(9064): 1498–1504.
Peto, R., M.C. Pike, P. Armitage, et al. 1976. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *British Journal of Cancer* 34(6): 585–612.
Scurti, V., M. Romero, and G. Tognoni. 2012. A plea for a more epidemiological and patient-oriented pharmacovigilance. *European Journal of Clinical Pharmacology* 68(1): 11–19.
Silverman, A., and A. William. 1986. *Human experimentation: A guided step into the unknown*. Oxford: Oxford University Press.
The World Bank. 1993. *World development report: Investing in health*. Washington, DC: World Bank/Oxford University Press.
Tognoni, G., and M. Bonati. 1986. Second-generation clinical pharmacology. *Lancet* 328(8514): 1028–1029.
Tognoni, G., and E. Geraci. 1997. Approaches to informed consent. *Controlled Clinical Trials* 18(6): 21–27.
Tognoni, G., V. Caimi, M. Tombesi, et al. 2012. Italian general practitioners of the Rischio e Prevenzione Study project. Primary care as a permanent setting for research. *Primary Health Care Research and Developement* 13(1): 1–9.
Topol, E.J. 2004. Failing the public health–rofecoxib, Merck, and the FDA. *New England Journal of Medicine* 351(17): 1707–1709.
Torres Goitia, J. 2008. *Desarrollo y salud*, 1st ed. La Paz: Artes Graficas Sagitario.
Toussaint, B. 2013. EU clinical trials regulation. *Lancet* 381(9879): 1719–1720.
Yusuf, S., R. Collins, and R. Peto. 1984. Why do we need some large, simple randomized trials? *Statistics in Medicine* 3(4): 409–422.

Contents

Contributors

Alejandro González-Arreola Gesoc A.C., Mexico DF, Mexico

Alonso Cerdán Secretaria de la Función Pública, Mexico DF, Mexico

Susie Dutra Comitê de Ética em Pesquisa, Fundação Hemominas, Belo Horizonte, Brazil

Corina Bontempo Duca de Freitas Coordenação de Pesquisa e Comunicação Científica, Fundação de Ensino e Pesquisa em Ciências da Saúde – FEPECS, Brasilia, Brazil

Duilio J. Fuentes-Delgado La Oficina General de Investigación y Transferencia Tecnológica (OGITT), Instituto Nacional de Salud of Perú, Lima, Peru

Nuria Homedes School of Public Health, Division of Management Policy and Community Health, University of Texas Houston Health Science Center, El Paso, TX, USA

William Saad Hossne BIOÉTICA, Centro Universitario São Camilo, São Paulo, Brazil

Gabriela E. Minaya-Martínez La Oficina General de Investigación y Transferencia Tecnológica (OGITT), Instituto Nacional de Salud of Perú, Lima, Peru

Susy Y. Olave-Quispe Unit of Executive Support, Agencia Española de Medicamentos y Productos Sanitarios, Madrid, Spain

Bruno R. Schlemper Jr. Medical School, University of West of Santa Catarina, Florianópolis, Brazil

Gianni Tognoni Consorzio Mario Negri Sud, Santa Maria Imbaro, Chieti, Italy

Antonio Ugalde Department of Sociology, University of Texas, Austin, TX, USA

Edith Váldez-Martínez Coordinacion de Investigacion en Salud (en el IMSS), Instituto Mexicano de Seguro Social (IMSS), Mexico DF, Mexico

Emma Verástegui Palliative Care, Instituto de Cencerologia, Mexico DF, Mexico

Chapter 1
Introduction

Nuria Homedes and Antonio Ugalde

1.1 The Origins and Development of This Project

The tension between the need to develop better treatments and protect human research participants is particularly acute in low and middle income countries, where the number of clinical trials with pharmaceuticals is on the rise and the systems to protect the research participants are relatively new and tend to be poorly developed. While, Latin American volunteers have been participating in international research and in clinical trials since the beginning of the twentieth century, most Latin American countries did not have regulatory agencies or a regulatory framework guiding the implementation of clinical research until the mid- 1990s or early 2000s.

As editors of an electronic bulletin aimed at improving the use of pharmaceuticals among the Spanish-speaking populations (www.saludyfarmacos.org), the editors of this collection became aware of reports describing violations of ethical research principles in Costa Rica and Argentina (Vargas 2006; Orchuela 2006a, b). Later, during meetings in Peru, Costa Rica and Argentina we learned that Colombian research participants did not understand the concept of informed consent; Argentinean psychiatric patients had been included in research projects without obtaining the informed consent from guardians or, in their absence, from the judiciary; and concerned Costa Ricans had unveiled problems with a very large clinical trial (over 13,000 participants) to study the effectiveness of a vaccine against human papilloma virus. Ethical research concerns are common throughout the world, but what was striking about the situation in Latin America was the insularity of the bioethicists and concerned researchers that were unveiling these issues. Researchers in other countries did not know about any of the cases described above.

N. Homedes (✉)
School of Public Health, Division of Management Policy and Community Health, University of Texas Houston Health Science Center, El Paso, TX, USA
e-mail: nhomedes@utep.edu

A. Ugalde
Department of Sociology, University of Texas, Austin, TX, USA
e-mail: augalde@utexas.edu

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_1,

The need to establish a network to monitor the ethical implementation of clinical trials in Latin America became obvious.

Using the network of collaborators and researchers that we had established through the publication of the bulletin and decades of research in Latin America, in 2007 we conducted an on-line survey to identify the existing ethics research infrastructure in 15 Latin American countries. We had a 100 % response rate, indicating that there was a strong interest in the topic and that people were eager to channel their interests and efforts in a more organized and structured fashion. We decided to capitalize on this interest and proposed the creation of a Latin American Network for Ethics and Pharmaceuticals (Red Latino Americana de Ética y Medicamentos or RELEM). RELEM's first product was a paper describing the results of the survey that was presented at an international meeting on Pharmaceutical Policy that was held in Zeist (Netherlands) in September 2007.

The RELEM initiative coincided with the interest of some international players who, aware that the applications for the commercialization of new drugs were increasingly including data gathered in low-and middle-income nations, became concerned about the manner in which trials were being conducted and of the quality of the information collected in low-and middle-income nations.

The reports about lack of informed consent to participate in a trial were particularly worrisome because it is conceivable that participants, unaware of their role in clinical research, could engage in behaviors that could, in turn, mask the results of the study, such as failure to report side-effects, inadequate compliance with the medical regimen, or self-medication with other OTC or prescription-drugs that are often sold without a prescription. Thus, when the human and civil rights of clinical trial participants are violated, the quality of the research suffers and might have a detrimental effect on the effectiveness and safety of the pharmaceuticals that are commercialized, a number of which tend to be primarily sold in high-income countries.

In 2008, with funding from the University of Texas, Salud y Fármacos (a US-based non-governmental organization), the Pan American Health Organization (PAHO), and WEMOS, a Dutch non-governmental organization, we organized the first Latin American Workshop on Clinical Trials and Ethics. The meeting was held in Buenos Aires (Argentina) in August 2008, and was attended by regulators, bioethicists, and clinical researchers from Argentina, Brazil, Costa Rica, Mexico and Peru. At the end of the meeting we had a research agenda, a Declaration (See Chap. 2), and a commitment to write a book describing the situation of clinical trials in the above listed Latin American countries. While not all participants in this and subsequent meetings are listed as authors in this volume, all of them contributed by sharing their thoughts, experiences, files and other archival documents, and reviewing the multiple versions of each chapter. We are deeply indebted to all of them.

The collection of articles in this book examines the evolution of the regulatory frameworks that guide the implementation of clinical trials in five Latin American countries and analyses clinical trials that highlight the main ethical issues that have arisen during their implementation. 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.

1.2 The Structure of the Book

The perpetual tension between advancement of scientific knowledge and the protection of clinical research subjects has led governments and professional associations to develop ethics codes to guide clinical research. After contrasting and assessing the different ethics codes that have been discussed and accepted in Latin America (Chap. 2), the authors assert that the ethical violations that have been documented in the region do not require perfect ethical codes and frameworks but the will of all actors in the clinical research process (i.e. pharmaceutical industry, governments, regulatory agencies, universities, clinical researchers, professional associations, research ethics committees) to protect the rights of clinical research subjects. The protection of these rights requires well-functioning ethics research committees that are free of financial conflicts, and adequate financing to monitor the recruitment of research subjects and the clinical research process.

The participation of Latin America in multinational clinical trials, along with the attractiveness of the region for international clinical research, is described in Chap. 3. The upsurge of clinical trials after the adoption of the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) and the approval of the Good Clinical Practice Guidelines from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH GCP) caught most national regulatory agencies unprepared. Most national, legal regulatory frameworks of clinical research are in constant change in attempts to improve the countries' competitiveness and to respond to the needs of the pharmaceutical industry while protecting the rights of the research subjects.

A general analysis of the clinical research regulations in Argentina and the country's participation in clinical trials since 2005 is provided in Chap. 4. Using the results of clinical trial inspections, and case studies of trials that have been questioned by researchers, the courts, the ombudsmen, the regulatory authorities and journalists, this chapter uncovers situations where trial researchers failed to obtain informed consent, duplicated patient records, and violated inclusion and exclusion criteria. About one-third of the clinical trials implemented in this country are conducted in the province of Cordoba, home to about 10 % of the country's population. Chapter 5 describes the political and regulatory context that caused clinical research to flourish there and how the inappropriate use of political influence, public infrastructure and the use of the public health system resulted in legal suits and fines against the clinical trial sponsor and the researchers. These two chapters illustrate how conflicts of interests within the research ethics committees, research centers, public hospitals and possibly the regulatory agencies, along with pressure from the groups who benefit from the implementation of the trials have facilitated the violation of scientific and ethical research principles.

The uniqueness of the Brazilian system of ethical review of clinical trials is described in Chap. 6. With the return to democracy, organized community groups

were empowered and became involved in the management of the public sector. The health sector was placed under the purview of the National Health Assembly, which in collaboration with stakeholders and community groups developed the regulatory framework for clinical research. In Brazil, all ethics research committees (CEPs), about 600, are institutionally based and all protocols classified as special projects, including all multinational clinical trials, have to receive the final approval of the National Commission for Research Ethics (CONEP). Although the system is not perfect, its history and structure, being the result of a broad consultative process and responding to the National Health Assembly, has enabled it to withstand the pressures of powerful stakeholders such as the pharmaceutical industry, academic clinical researchers and political leaders. Brazilian bioethicists have had a significant impact in the international arena, especially in the discussions within the World Medical Assembly about the use of placebo. Despite all of these efforts, as pointed out in Chap. 7, the clinical trials that are conducted in Brazil do not reflect the research priorities of the Brazilian Ministry of Health.

The organization and quality of the Costa Rican health care system has attracted the attention of clinical research sponsors since the 1960s. This small country conducts a disproportionate number of clinical trials, especially involving pediatric populations, which are conducted by a handful of clinicians. Despite its level of involvement in multinational clinical research, the regulatory framework remains incomplete, mainly due to the tensions among four different interest groups; (1) the Ministry of Health; (2) physicians involved in clinical research; (3) members of the Legislative Assembly who oppose the use of public facilities for private gain and who advocate for the protection of the rights of clinical research subjects; and (4) members of the Costa Rican Social Security Institute and non-governmental organizations who oppose the use of public resources for private gain. Using publicly available documents, including reports from the Legislative Assembly and Supreme Court decisions, Chap. 8 describes the progressive privatization of clinical research, the ups and downs in establishing an appropriate regulatory framework, and the conflicts among the four groups mentioned above.

Guanacaste is the Costa Rican region where researchers – with the support of the USA National Cancer Institute – have been studying cervical cancer and its prevention since 1985. Undoubtedly the results of these studies are of high scientific and economic value, but they have not been free of controversy. Chapter 9 describes the complexities surrounding longitudinal clinical research projects, and the conflicts of interest and ethical violations that have been uncovered during 20 years of research in this region. Despite ethical concerns with the informed consent forms, and in the process of recruiting participants, some of these studies were approved by three research ethics committees. Most of these irregularities occurred under the oversight of international research sponsors.

Mexico is an attractive country for clinical trials, but almost 30 years after adopting the General Health Act and the Regulations of the General Health Act for Health Research (RLGSIS), the people of Mexico lack the certainty that their rights as participants in clinical research are being fully protected. Chapter 10 describes some of the challenges Mexico needs to overcome to comply with

international ethical standards. One of the major problems relates to the informed consent process, and the readability of informed consent forms. Moreover, the authors of Chap. 11 illustrate the importance of integrating the cultural and social norms when providing health care services, which, in the case of Mexico, may include the incorporation of members of the family when cancer patients are asked to participate in clinical trials.

Peru was one of the first countries to regulate pharmaceutical research (1981) but the Ministry of Health did not register any trial until 1995. The rapid growth in clinical trials and clinical research participants that occurred in the late 1990s and early 2000s led the Ministry of Health to revise the system for the authorization and supervision of clinical research in 2004. The authors of Chap. 12 participated in this review process and describe their experience, the content of the new regulations, and the tension between the different stakeholders. The new regulations, despite having been praised by several international groups, and coinciding with a change in government resulting from a national election, were changed a few months after their approval. This chapter describes the forces that led to the most recent regulatory changes and the remaining challenges for the protection of human research subjects.

In the closing chapter (Chap. 13) we present the main similarities and differences regarding the regulatory process and the implementation of clinical trials that have been identified in the five countries discussed in this book. We conclude by acknowledging that today the human rights of many clinical trial participants – the majority of whom are poor - are being violated in Latin American, and that the incentives to expedite the conclusion of the trials might be negatively affecting the quality of the data collected. The ethical review system requires a major overhaul, and it is unlikely that the pharmaceutical industry will take the lead in making the necessary changes. The 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 independent from the sponsors that do not have financial incentives. It may take some time before the change occurs, but it will happen.

1.3 Concluding Remarks

The information regarding clinical trials that is made accessible to the general public is very limited. The pharmaceutical industry requires all parties involved in any aspect of the research process to conceal most of the information, well beyond those aspects that could be considered industrial secrets. Governments are often conflicted, seldom cooperate, and frequently disregard the legitimate questions and concerns raised by civil society. The collective experience of the contributors to this volume is that formidable barriers preclude us from having a comprehensive view of the ethical problems surrounding the implementation of clinical trials in Latin America; conducting research in this field has proven to be very difficult, and the availability

of resources to examine the ethical behavior of powerful corporations and their supporting governments is extremely scarce. Nevertheless, little by little, with the assistance of those who at one time or another witness the actions and consequences of those who put scientific research or economic benefits above the lives and dignity of research participants, researchers with a great amount of determination and patience will continue to pursue ways to document the abuses and propose solutions. This book is a small contribution towards this effort. We have to keep in mind that it took almost 40 years to find—and it was by an incredible chance—the abuses/atrocities that USA researchers with the assistance of local physicians committed during clinical trials in Guatemala (Reverby 2012), and that many unresolved issues remain regarding the clinical trials that the US Army carried out at the Edgewood Arsenal during the Cold War (Khatchadourian 2012). 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.

Acknowledgements This book would not have been possible without the help and encouragement of the members of the Latin American Network for Clinical Trials and Ethics, and the financial and moral support from WEMOS, Salud y Fármacos and the University of Texas. Our gratitude is extended to Dr. Hernán Collado, one of the persons in Costa Rica that throughout the years has fought tirelessly to protect the human rights of those who knowingly or unknowingly participated in clinical trials in his country and provided us with difficult-to-obtain documents, including reports from the National Assembly, Court decisions, and personal letters from health authorities. Liliana Virginia Siede also helped in tracking government and administrative reports and Court decisions that helped writing the Argentinean chapters. Dr. Ana Pérez from The National Administration of Drugs, Foods and Medical Devices of Argentina (ANMAT) helped and encouraged us in our research until weeks before her untimely death. ANMAT lost a dedicated and courageous researcher and we a dear and trusted friend. A special thanks to Olive Roen RN, DrPH and Jean Setzer Ph.D. who translated the chapters that had originally been written in Spanish, and the editorial work of Kamala Platt, Ph.D.

References

Khatchadourian, R. 2012. Operation Delirium. *The New Yorker*, December 17. http://www.newyorker.com/reporting/2012/12/17/121217fa_fact_khatchadourian?printable=true. Accessed 31 Jan 2013.

Orchuela, J. 2006a. Denuncias for investigación de medicamentos sin consentimiento en hospital neuropsiquíatrico de mujeres [Accusations of research on women in a neuropsychiatry hospital without informed consent]. *Boletín Fármacos* 9(2): 126–129.

Orchuela, J. 2006b. Investigaciones clínicas con medicamentos y vacunas en hospitales públicos de Córdoba y Santiago de Estero fuertemente cuestionadas [Vaccine and pharmaceutical research conducted in public hospitals in the provinces of Cordoba and Santiago de Estero is being severely questioned]. *Boletín Fármacos* 9(1):100–105.

Reverby, S.M. 2012. Ethical failures and history lessons: The U.S. Public Health Service Research Studies in Tuskegee and Guatemala. *Public Health Reviews* 34(1). http://www.publichealthreviews.eu/upload/pdf_files/11/00_Reverby.pdf. Accessed 31 Jan 2013.

Vargas, E. 2006. Costa Rica: Epidemia de Ensayos Clínicos [Costa Rica: Clinical trials epidemic]. Special report. *Boletín Fármacos* 9(3): 85–92.

Chapter 2
A Review and Critique of International Ethical Principles

Nuria Homedes and Antonio Ugalde

History shows that health professionals who conduct biomedical research continually confront the tension between the advancement of scientific knowledge and the protection of human subjects. There have been spectacular advances in the science of medicine during the past 150 years, but the associated disregard and active malfeasance towards the participants in some experimental situations have led to many attempts to protect study volunteers. Unfortunately, ethical violations continue in clinical research, possibly more so in developing countries where regulations to protect human subjects are not fully in place. This chapter reviews the internationally accepted Codes of Ethics, their relevance and potential for low- and middle-income countries, and the issues that continue to be discussed by bioethicists when they try to agree on standards for clinical research in the developing world.

2.1 The Nüremberg Code and Its Predecessors

The Nüremberg Code (1947) is frequently identified as the first document to discuss ethical rules for human beings. The Code was written in response to the behavior of some researchers in the mid twentieth century and the lack of ethical guidelines. Vollmann and Winau (1996) note that the first attempts to protect study participants date to the end of the nineteenth century. At that time, most research was directed towards understanding the pathophysiology of disease and the response of the individual, with research into disease prevention and treatment following at a later date. Most of these studies took place with hospitalized patients, frequently without their

N. Homedes (✉)
School of Public Health, Division of Management Policy and Community Health, University of Texas Houston Health Science Center, El Paso, TX, USA
e-mail: nhomedes@utep.edu

A. Ugalde
Department of Sociology, University of Texas, Austin, TX, USA

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_2,

consent. Research was also sometimes conducted on prisoners. In 1891, the Prussian Minister of the Interior sent an official letter to all prisons forbidding the use of tuberculin as a treatment for tuberculosis without previously obtaining informed consent from all prisoners.

A study by Dr. Albert Neisser was one of the most controversial cases of that time. In 1898, without obtaining informed consent, he injected serum from patients with syphilis into prostitutes who had been hospitalized for other reasons. This case was investigated by the Prussian public prosecutor, and was discussed for some time in the Prussian Parliament and among prominent scientists, many agreeing with Dr. Neisser. Later, a report was requested from the Scientific Medical Office of Health. The legal argument against Dr. Neisser was not about questionable science, but that consent had not been obtained from his study participants. He was found guilty by the Royal Disciplinary Tribunal, and fined. Discussion continued about issues of autonomy (the right of an individual to make a personal decision without any type of coercion) and beneficence (do only good), and that there was a need for studies to be first conducted with animals, then with the researchers themselves, and only then with other human beings who had freely given their informed consent.

In 1900, the Prussian Minister for Religious, Educational, and Medical Affairs issued the first ethical standards to govern "non-therapeutic" research in hospitalized humans. The standards included: (1) obtaining informed consent, and forbidding research on children and persons who, for whatever reason, did not have the capacity to understand the risks of the proposed experiment and give their full consent to participate; (2) that the research would take place with the authorization of the director of the center, who would be held responsible for any ill effects on the patient, and (3) that compliance with these requirements and other circumstances related to the study would be documented in the medical record. In 1902, Albert Moll, a German psychiatrist, developed a contract to guide the physician-patient relationship, incorporating areas of beneficence, autonomy, and informed consent (Vollmann and Winau 1996).

In 1931, the German government issued detailed ethical guidelines for research with human subjects that distinguished between therapeutic and non-therapeutic research. At that time, Germany had the most advanced regulations for research with humans, but they did not prevent the criminal experiments on concentration camp prisoners, for which Germany was condemned during the Nüremberg Trials. Several of these guidelines were strengthened and included in greater detail in the Code of Nüremberg and in the Declaration of Helsinki.

2.1.1 The Nüremberg Code

During the second world war, both Japan and Nazi Germany conducted cruel experiments on human beings, causing death for many and permanent injury to others. At the end of the war, the United States Government granted immunity from prosecution to the Japanese in exchange for information about the results of the studies. German scientists, however, were judged at trials for war crimes. With the intention of avoiding similar situations in the future, the Nüremberg Military

Box 2.1: Summary of the Nüremberg Code

1. Informed consent: given voluntarily, without pressure, based on access to and understanding of the information about the study. The principal investigator is solely responsible for the quality of the informed consent process
2. The research will provide benefits to society, which would otherwise not be available
3. The research will be designed based on animal studies and on knowledge of the natural history of the disease
4. All possible efforts will be made to reduce any physical or mental suffering of the volunteers
5. No experiments will take place if it is known in advance that they may cause death or disability
6. Risks taken must not exceed the scale of the problem to be solved
7. Precautions must be taken to protect volunteers from any possible danger, disability, or death
8. Only trained personnel may conduct research
9. The volunteer must be able to withdraw from the study at any time
10. The researcher must be willing to end the study at any time if the welfare of a volunteer is in jeopardy

Source: Nüremberg Code (see Appendix 1)

Tribunal issued a 10 point document, known as the Code of Nüremberg (see Box 2.1). The Code had little resonance among researchers at first, as they considered it was written in response to situations of extreme brutality, far removed from customary medical research. The Code became more important as ethical violations increased, but many researchers felt that it was too rigid and that it was almost impossible to meet the conditions (Faden et al. 1996).

The Code of Nüremberg, although never formally adopted by any country, has since been very influential in the development of ethical principles for research with human subjects.

2.2 The Declaration of Helsinki

The World Medical Association (WMA), established in London in 1946, condemned the actions of the Nazi physicians and published the International Code of Medical Ethics in 1949, based on the Declaration of Geneva. The document was vague and subject to different interpretations. It was amended in 1968, 1983, and 2006. It is short, and specifically addresses the duties of physicians in general, to patients, and to colleagues (WMA no date).

In 1953, stimulated by the war horrors revealed during the Nüremberg Trials, WMA members asked the Medical Ethics Committee for recommendations to guide physicians who were – or would be – conducting biomedical research involving human subjects. After several years of discussion and study, a draft declaration was prepared, revised, and adopted in 1964 at the 18th General Assembly of the WMA in Helsinki, Finland (WMA no date). The first Declaration of Helsinki had 11 basic principles, but it has since been revised and expanded several times – in 1975, 1983, 1989, 1996, 2000, and 2008. In addition, the WMA issued clarifications to Article 29 in 2002, and Article 30 in 2004. The most recently amended 2008 version has 35 paragraphs.

Both the Code of Nüremberg and the 1964 Declaration of Helsinki established that the welfare of the individual was more important than scientific advancement. The 1964 Declaration of Helsinki is weaker than the Nüremberg Code in the area of informed consent, because the researcher may be exempted from the obligation to obtain informed consent, but the responsibility of the physician as a protector of the patient's health and well-being is increased. Research is permitted on persons who are not able to give informed consent themselves (children, captives, and people with mental disabilities) if and when consent is given for them by their legal representative (Leaning 1996). The Declaration of Helsinki distinguishes between therapeutic and non-therapeutic research, and clearly states the obligation to respect ethical principles when conducting therapeutic experimentation.

Violations of ethical principles continued, including in projects financed by government agencies (Beecher 1966; Brandt 1978; Katz et al. 2003). In response to these abuses, the Declaration of Helsinki of 1975 (approved in Tokyo) is more specific and almost twice the length of the original version, stating explicitly that the protection of the individual is above any community interest (paragraph III. 4. 1975), and conditions the publication of the study results to the prior approval of the research protocol by an ethics committee and adherence to the Declaration of Helsinki. The revisions of 1983 (Venice) and 1989 (Hong Kong) focused on the consent of minors (I. 11. 1983), and the independence of ethics committees and their conformity with national laws (I. 2. 1989), respectively. The 1996 revision (South Africa) introduced a controversy, which has increased over time and is still far from being resolved – the use of placebo. The 1996 amendment limited the use of a placebo to cases where no approved procedure is available, allowing placebo control groups in studies of pathologies where a diagnostic method or therapy currently doesn't exist (II. 3.1996) (de Abajo 2001). The Food and Drug Administration (FDA), USA, was concerned about the limitation on the use of placebos, and has still not accepted either the 1996 revision or any of the subsequent revisions. The FDA continues to operate from the 1989 Declaration of Helsinki (FDA 2001; Temple 2003).

The 1996 and 2000 revisions were in response to a situation arising in the mid1990s. Studies on the prevention of the transmission of HIV/AIDS in Africa were designed with a placebo arm, but in industrialized countries the control group was given an approved treatment. In 1997, Lurie and Wolfe (1997) published an article condemning the use of placebo in 15 of 18 clinical trials on the perinatal

transmission of HIV, which had been – or were being conducted – since 1994. All 15 trials were taking place in low- and middle-income countries and received financing from the National Institutes of Health (NIH), an agency of the USA federal government, while control groups for trials in the USA and in Thailand received treatment with ACTG076.[1] ACTG076 is a regime for the administration of zidovudine, a standard treatment adopted in industrialized countries in 1994, which reduced the perinatal transmission of HIV by two thirds.

Lurie and Wolfe (1997) criticized the use of placebo for both scientific and ethical reasons. In their opinion, clinical trials with placebo controls did not contribute to the advancement of science as much as other study designs would have contributed; they considered this to be an ethical problem. Of greater importance, however, was the establishment of two ethical standards: one for the industrialized world, and another for low- and middle-income countries. Study sponsors justified placebo use in low- and middle-income countries because in general these patients had no access to treatment and probably would not have access to treatment in the near future. In other words, study participation did not imply any additional risk. The counter argument was that the lack of access to treatment was a purely economic issue which, when applied to clinical research, only encouraged the exploitation of vulnerable residents of low- and middle-income countries who, regardless of the result of the clinical trial, would contribute to the advance of science. However, if the procedure studied had positive results, the only participants likely to benefit would be residents of high-income countries, since for the rest the new product would be unaffordable. The unequal distribution of risks and benefits is a violation of the principle of justice, discussed in the Belmont report (see below). Accepting the double standard may be interpreted as an admission that people in low socio-economic circumstances do not have a right to treatment. Placebo control is a subject which has been intensively discussed and which continues to be controversial. Some scientists, including members of the NIH, the FDA, and the European Medicines Agency (EMA, formerly EMEA) (EMEA 2002), defend the need for placebo controlled studies for methodological reasons related to: (1) the sensitivity of clinical trials; (2) efficiency – they require smaller sample sizes, less study time and therefore lead to faster commercialization of the new drug; and (3) the fact that, in many studies, in the long term, the use of placebo does not have negative consequences for participants in the placebo group – for example, studies of treatments for allergies, insomnia, anxiety, etc. (Temple and Ellenberg 2000). At the other extreme are those who ask the FDA to revise its policies for placebo-controlled clinical trials when there are other effective treatments (Ramsay 2000), and who say that even if scientific advances require the use of placebos, this causes a direct confrontation between science and ethics (Rothman et al. 2000), and also creates a clash between the benefits to society *vs.* the rights of the individual.

[1] The National Institutes of Health (NIH), USA, pressured Harvard University researchers to use a placebo for the control group in the Thailand study.

The American Medical Association (AMA), which did not support the 1996 revision of the Declaration of Helsinki, in 1997, suggested another revision of the Declaration and, once the proposal was accepted during the General WMA Meeting in Hamburg, formed a working group, organized several meetings for discussion, and published various editorials and articles -both for and against- the proposed changes (Brennan 1999; Loff and Black 2000; Rothman et al. 2000; Stockhausen 2000; Zion et al. 2000). At the WMA meeting in Edinburgh in the year 2000, a new version of the Declaration of Helsinki was approved without the consensus of all participants (Nicholson 2000). The new version included the following points: (1) reference to the concept of social justice was included for the first time, establishing that "[m]edical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stands to benefit from the results" (paragraph 19); (2) research must not take place in any person who is "...legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor...unless the research is necessary to promote the health of the population represented, and this research cannot instead be performed on legally competent persons" (paragraph 24); (3) "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists." (paragraph 29); (4) "At the conclusion of the study, every patient entered into the study should be assured access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study." (paragraph 30); (5) "The researcher should also submit to the ethics committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects." (paragraph 13); (6) "...each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal..." (paragraph 22); and (7) the Declaration addresses "medical research", eliminating any distinction between therapeutic and non-therapeutic research (Klimovsky et al. 2002). Predictably, the most contentious changes were the limitations on the use of placebo (paragraph 29); that the study population should have the possibility to benefit from the study results (paragraph 19); and that there is an obligation to provide access to the best procedure at the end of the study (paragraph 30).

The adoption of this revision did not resolve anything; it actually deepened the differences in perspective between high and low- and middle-income countries while the USA was accused of moral imperialism (Angell 1988; Benatar 1998; Rothman et al. 2000; Dawson and Garrard 2006; Tealdi 2006; Garrafa and Lorenzo 2008). Eventually, in response primarily to pressure from the United States and the pharmaceutical industry (Wolinsky 2006), a clarification to paragraph 29 was added in 2002, to specify circumstances when a placebo could be used when other therapies were available. Another clarification, this time to paragraph 30, was added in 2004, stating that study protocols were to include a section describing the conditions for the

provision of the best methods of prevention, diagnosis and treatment. This section would be included in the protocol and would be evaluated by the ethics committees. As predicted (O'Neil 2008), these clarifications were not well received by the low- and middle-income countries, especially in Latin America, because the experts (Tealdi 2006; Garrafa and Lorenzo 2008) saw them as facilitating placebo use, and allowing ethics committees to decide the circumstances when communities would have access to the study procedure if it were shown to be the best available.

In this atmosphere, in May 2007, a working group was formed to once more revise the Declaration of Helsinki. Revision proposals were circulated and three workshops organized: one in Helsinki in March, 2008, and the others in Cairo and São Paulo in August, 2008. After evaluating the proposed revisions, the Brazilian Ministry of Health rejected the revision on the use of placebos, and the Medical Confederation of Latin America and the Caribbean (CONFEMEL) rejected the proposed changes to the Declaration because the clarifications to paragraphs 29 and 30 were now in the text of the Declaration (paragraphs 32 and 33 in the Declaration of Helsinki, 2008), and in their view they violated human rights. However, in Seoul in 2008, the new version of the Declaration of Helsinki was approved, with Brazil and 23 other countries voting against it.

Even with these changes, the FDA did not accept the new version of the Declaration of Helsinki. In 2008, as discussed below, the FDA announced that it was not necessary for clinical trials conducted outside the United States to comply with the 1989 Declaration of Helsinki, only with Good Clinical Practice guidelines of the International Conference on Harmonisation (ICH GCP 1996). During a scientific congress organized by the Bioethics Network for Latin America and the Caribbean (coordinated by UNESCO), ten Latin American countries signed the Declaration of Cordoba, rejecting the 2008 Declaration of Helsinki and proposing to adopt the ethical standards of the UNESCO Universal Declaration of Bioethics and Human Rights, approved by 191 countries in 2005 (Redbioética-UNESCO 2008). In addition, the Brazilian Federal Council of Medicine (Conselho Federal de Medicina 2008) issued a prohibition for physicians conducting medical research with human subjects to use placebos when an effective treatment was available for the health problem under investigation.

There is concern that the controversy over the use of placebo and post-study access to the best procedure might erode the influence of the Declaration of Helsinki as a worldwide reference document for research involving humans (Garrafa and Lorenzo 2008; Kimmelman et al. 2009; Rid and Schmidt 2010). In most countries of the world, the laws and regulations related to biomedical research include the need to implement the Declaration of Helsinki, but over time this could change. Some members of the WMA have spoken against governments mandating compliance with the Declaration of Helsinki for two reasons: (1) the Declaration included higher standards than those required by the laws and regulations of some countries; and (2) nations could not change their legal framework in response to the frequent revisions of the Declaration of Helsinki (Wolinsky 2006).

Less frequently discussed clauses in the 2008 Declaration are two clauses that will lead to improved transparency of clinical trials: requiring the registration of

the protocol in a public data base before the recruitment of study participants (paragraph 19) and the publication of the results (paragraph 30) (Krleza-Jeric and Lemmens 2009). The pharmaceutical industries do not welcome the registration requirement because they claim it threatens their intellectual property rights and could delay the start of clinical trials (Normile 2008).

2.3 International Covenants on Civil and Political Rights, and on Economic, Social and Cultural Rights

In 1966, the General Assembly of the United Nations adopted the International Covenant on Civil and Political Rights, which states in Article 7: "No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation" (United Nations 1966a). This clearly establishes the relationship between research ethics and human rights (Tealdi 2006). Article 2.1 of the International Covenant on Economic, Social, and Cultural Rights asks countries "individually and through international assistance and co-operation, especially economic and technical," to protect the human rights of their population, especially for the most vulnerable and marginalized groups (United Nations 1996b). And the Declaration of Human Rights, Article 27(1), states that "Everyone has the right ... to share in scientific advancement and its benefits." (United Nations 1948; Toebes 1999).

2.4 The Belmont Report, 1979

Concerned about the ethical violations that occurred in the USA between 1963 and 1972, the federal government established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission operated between 1974 and 1978, and issued the Belmont Report on the basic principles for research involving human subjects (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979). The report was based on three basic principles: respect for the individual (informed consent and voluntary participation); beneficence (do not harm, maximize possible benefits and minimize possible risks), and justice (equitable distribution of risks and benefits in a population). Many of the proposals made by the Commission have been incorporated into the laws and regulations which govern research in the USA, especially in the areas of informed consent, the composition and operation of ethics committees, and the system to protect vulnerable populations (infants and young children, pregnant women and their fetus, prisoners, institutionalized people, and people with mental disorders).

Part of the Belmont Report was incorporated into the 1991 Federal Policy for the Protection of Human Subjects, known as the Common Rule, which was accepted by all the agencies of the federal government that could be affected by the policy. The

FDA requirements for the approval of new medications are consistent with this policy, especially in regard to obtaining informed consent and prior review by an ethics committee (Emanuel et al. 2003:27).

2.5 The CIOMS/WHO Guidelines

After the approval of the 1964 Declaration of Helsinki, the World Health Organization (WHO) asked the Council for International Organizations of Medical Sciences (CIOMS), a non-governmental organization founded in 1949 to collaborate with the United Nations, to transform the Declaration of Helsinki into a guide for WHO member countries, primarily for low- and middle-income countries. In 1982, CIOMS published the Proposed International Ethical Guidelines for Biomedical Research Involving Human Subjects, and, in 1993, the International Ethical Guidelines for Biomedical Research Involving Human Subjects, containing 15 points with commentaries. In 2002, in response to the crisis generated by AIDS-related research studies (see above), CIOMS published a revision of the ethical guidelines containing 21 points with commentary (CIOMS 2002; Fischer 2006).

The CIOMS guidelines were the first to address the socio-economic and political environments of emerging and newly independent countries, and taking into consideration that research is necessary, proposed the use of the guidelines to protect both the participants and the research itself. The first three guidelines relate to the scientific justification of the study and the review by ethics committees, establishing that studies conducted in various countries must be approved in the country of origin (Fischer 2006).

Guidelines 4–7 discuss the parameters to be observed when obtaining informed consent (voluntary; the right to withdraw from the study; an explanation that it is a research study and may not benefit the participant; confidentiality; an explanation of the research design, including issues of randomization and double-blind studies; a description of the risks and benefits; the sources of funding; any compensation for study participants; the right to know the results; the availability of the product after the conclusion of the study; and the obligation of sponsors and researchers to avoid unjustified deception, undue influence, or intimidation, etc.). CIOMS clarifies that informed consent is a process, and that patients should have time to study the information provided by the researchers and to question anything before they grant their consent to participate in the study. The list of requirements considered sufficient by CIOMS guidelines is shown in Box 2.2.

Guideline 8 discusses the risks and benefits that may be considered acceptable, and Guideline 9, how to protect vulnerable populations, including people living in low socio-economic conditions, those with low educational levels, employees, the disabled, people with chronic or debilitating illnesses, indigent groups, residents in homes for aged persons, pregnant women, prisoners, university students, and inmates in state facilities (Macrae 2007).

Guideline 10 establishes that the sponsor or investigator must do everything possible to ensure that the studied procedure, within reason, is accessible and

Box 2.2: Summary of the Rules for Informed Consent, Council for International Organizations of Medical Sciences (CIOMS)

- Discuss the study objective and the reason why the individual is asked to participate
- Assure that participation is voluntary
- Explain that a study participant may withdraw from the study at any time
- Explain the objective of the study in greater detail
- Describe the study design in a way that the participant can understand it
- Discuss the length of time necessary for study participation
- Discuss any compensation provided to participants
- Describe how participants can learn about the study results
- Explain that personal information is confidential, with safeguards to prevent access to information on individuals
- Confirm that an ethics committee has approved the study
- Give information about possible risks
- Discuss the potential benefits for the individual and the community
- Discuss the possibility of access to treatment after the conclusion of the clinical trial
- Present alternative treatment or medication options to the study material
- Explain any possible future use of information or samples obtained in this study
- Explain the role differences between a personal physician and a physician conducting research
- Describe the medical treatment to be provided during the study
- Explain the measures to be taken if the participant suffers any adverse effects as a result of study participation
- Explain the compensation to be offered to the participant if he or she suffers an adverse event attributable to his/her participation in the study

Source: Adapted from Macrae (2007).

benefits the population or community in which it has been studied.[2] Guideline 11 states that the use of placebo is justified only in the following circumstances: (1) when an effective intervention does not exist; (2) when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms; and (3) when it is necessary to establish

[2] Levine's argument justifies the use of the best treatment for control groups that is available in developing countries. According to Levine, comparing new treatments with the best available in industrialized countries would not help to answer the questions of poorer countries (Klimovsky et al. 24).

the efficacy of a treatment and the placebo would not add any risk of serious or irreversible harm to the study participants (Emanuel et al. 2003:27). Guideline 12 requires the risks and the benefits of the study to be equitably distributed among the community and at the global level (Fischer 2006).

Guidelines 13–17 discuss the participation of vulnerable groups and establish that these populations may participate only under certain circumstances. These circumstances include the participants' benefiting from the results of the studies, and the studies should be relevant only to people with their own medical conditions; therefore the studies can only be conducted in these population groups. Guideline 18 addresses information confidentiality; 19 establishes the need to offer compensation in case of adverse effects, and the final two guidelines strengthen the quality of the ethical review in low- and middle-income countries and place the responsibility for complying with the guidelines on the sponsors and the host countries.

2.6 Good Clinical Practice Guidelines

Until recently, the regulatory agencies of the different industrialized countries used a variety of processes to determine if a product should be marketed within their jurisdiction. In 1990, the European Federation of Pharmaceutical Industries and Associations (EFPIA) convened a meeting in Brussels to discuss the possible collaboration of the USA, Japan and Europe to develop joint standards for the approval of medications. The regulatory agencies agreed, and established the International Conference for the Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), with an office in Geneva, Switzerland.

The ICH published several documents related to the evaluation of the safety, quality, and efficacy of medications, among them one, which addressed clinical trials: The Guide to Good Clinical Practices (GCP), published in 1996 (Mercosur 2012; Williams 2005). During the same year, Mercosur[3] published resolution number 126/96, which is a technical document on how to verify compliance with good clinical practices. This document offers guidance to Mercosur member countries, which decide how to incorporate it in their legislations. Compliance with good clinical practices has also been discussed at the regional level. The regulatory agencies, under the leadership of the Pan American Health Organization, established the Pan American Network for Drug Regulatory Harmonization (PANDRH) and one of its working groups revolves around issues of Good Clinical Practices. In March 2005, during the IV Pan American Conference on Drug Regulatory Harmonization, the document Good Clinical Practices: Document of the Americas was officially adopted (Red PARF 2005).

On October 27, 2008, the FDA announced that it was no longer necessary for clinical trials conducted outside the United States to comply with the Declaration of

[3] Mercosur or the Southern Common Market is an economic and political agreement between Argentina, Brasil, Paraguay, Uruguay and Venezuela that was founded in 1991.

Helsinki, that compliance with the GCP would be sufficient (Department of Health and Human Services 2008). According to the GCP, vulnerable patients are those whose willingness to participate may be affected by the perception of the benefits to be obtained as a result of participation, or by the threat of reprisals from their superiors, which may include the following groups of people: students in the health professions, employees in the health sector, members of the military, prisoners, people with chronic or terminal illnesses, residents of homes for the aged, people of low economic resources, ethnic minorities, people needing emergency care, infants and children, and those who cannot give informed consent (Fischer 2006).

According to the FDA, the decision to eliminate the need to comply with the Declaration of Helsinki and to adhere to GCP was due to a need to assure the quality of the information received from low- and middle-income countries, to avoid the confusion caused by the frequent revisions to the Declaration of Helsinki, and to the concern that future revisions may conflict with USA laws and regulations. This justification does not explain why the change affected only studies carried out in low- and middle-income countries, especially since most of these countries have adopted laws and regulations which include the principles of the Declaration of Helsinki. In the opinion of critics, the FDA action is consistent with its interest in conducting placebo-controlled studies in low- and middle-income countries. It seems that this was an independent decision in isolation from the other authors of GCP, and is curious because the GCP document states that clinical trials must be in accordance with the ethical criteria presented in the Declaration of Helsinki.

Kimmelman et al. (2009) compared the GCP with the Declaration of Helsinki and voiced concern because the GCP had neither the breadth nor the depth of the Declaration, and could leave participants in biomedical research unprotected. The major objective of the GCP is to harmonize the registration of medications. It is not a guide of ethical principles for clinical trial sponsors and researchers. Box 2.3 presents clauses of the Declaration of Helsinki, which are not included in GCP. Another problem is that the GCP was developed only by the regulatory agencies and representatives of the pharmaceutical industry in the USA, Europe, and Japan, while the Declaration of Helsinki is endorsed by the WMA, which at that time represented the medical associations of 85 countries from all around the world.

Box 2.3: The Declaration of Helsinki *vs.* Good Clinical Practice (ICH GCP[4])

In a comparison between the Declaration of Helsinki, 2008, and Good Clinical Practice (GCP), it was found that the following items are not included in the GCP:

- Requirement for researchers to give information about study financing, sponsors, and conflicts of interest to ethics committee members and to the study participants

(continued)

[4] ICH GCP: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Good Clinical Practice.

Box 2.3: (continued)

- Publication of the study design (for example, through public records)
- Assurance that the study objectives are relevant for the study population
- Limitations on the use of placebo
- Assurance that there will be access to procedures or therapies after the conclusion of the clinical trial
- Accurate reports of results, with negative results available to the public

Source: Kimmelman et al. (2009).

2.7 The Universal Declaration on Bioethics and Human Rights (UNESCO)

The Universal Declaration on Bioethics and Human Rights is the first bioethics document ranked as a non-binding international agreement, and was approved by the 191 countries participating in the UNESCO 33rd. session of the General Conference, on October 2005. It is a succinct document of 28 Articles covering many topics while omitting detailed definitions or clarifications. It was prepared by an intergovernmental commission, and to some extent reflects what is feasible from a political point of view. Andorno (2007) says that the status of a non-binding agreement enabled many countries to sign the document since this type of document carries significant moral and political rather than legal weight. Several authors agree that the most important value of this document is that is has been supported by 191 governments (Andorno 2009; Gunson 2009).

Andorno (2002, 2007, 2009) suggests that from the point of view of bioethics, an agreement on basic values is the foundation for future laws that will provide a structure for implementation. From his perspective, respect for human dignity is closely tied to the enjoyment of human rights. Others have criticized the use of a human rights framework because of its ideological base, which does not have universal acceptance and is rarely used by bioethicists (Landman and Schüklenk 2005). Faunce and Nasu (2009) agree with Andorno that the principles underlying the bioethics and human rights frameworks are not irreconcilable, although bioethics is not a set of rules, but rather a gathering of ideas, debates, and ways of thinking, while "rights" implies systems to make sure certain principles are met. These authors continue by saying that in order to reconcile both perspectives, documents need to clearly explain the intersection between bioethics and international law, and must include more detail than in the UNESCO Declaration. Gunson (2009) thinks that the most prominent values in the UNESCO Declaration are human dignity, human rights, and solidarity, although "solidarity" is not defined, but rather is implied. Box 2.4 shows that a high proportion of the Articles in this Declaration include clauses reflecting the need to respect and the wish to understand different perspectives, which, for Gunson, is a form of solidarity and respect for human dignity.

Box 2.4: Summary of the Universal Declaration on Bioethics and Human Rights

- Respect for human dignity and human rights (section II, article 3.1)
- Priority to individual interests and well-being over the interests of science and society (section II, article 3.2)
- Beneficence, not maleficence (section II, article 4)
- Autonomy (section II, article 5)
- Informed consent (section II, article 6)
- Protection of persons who cannot give informed consent (section II, article 7)
- Special attention to vulnerable people (section II, article 8)
- Privacy and confidentiality (section II, article 9)
- Equality, justice, and equity (section II, article 10)
- No discrimination or stigmatization (section II, article 11)
- Respect for cultural diversity and pluralism (section II, article 12)
- Solidarity and cooperation (section II, article 13)
- Access to health services and to essential medications (section II, article 14)
- Sharing benefits (section II, article 15)
- Protection of future generations (section II, article 16)
- Protection of the environment, the biosphere, and biodiversity (section II, article 17)
- The need for professionalism, honesty, integrity, and transparency in decision-making related to bioethical issues (section III, article 18)
- The need for ethics committees to be independent, multidisciplinary, and pluralist (section III, article 19)
- Appropriate use of measurement systems and risk management in the biomedical area (section III, article 20)
- The need for justice in transnational research (section III, article 21)

Source: Modified by the authors from Adorno (2007), p 151.

The UNESCO Declaration has been criticized many times, both for the process of its development and for its content. UNESCO has been criticized also for impinging upon the territory of another United Nations agency, The World Health Organization, which could have undertaken this effort (Landman and Schüklenk 2005; Williams 2005; Trotter 2009). In reply to the last criticism, Andorno (2007) said that it is not unusual to have some overlap between the different United Nation's agencies. UNESCO has been working with bioethics issues since 1993, when it established the International Bioethics Committee (IBC) with 36 members appointed by the UNESCO Director General. In 1998, the Intergovernmental Bioethics Committee (IGBC) was added with representatives from 36 member states elected by the UNESCO General Assembly; IGBC's role was to advise the IBC and review documents before publication, although IBC is not obligated to

incorporate the IGBC suggestions (Snead 2009). UNESCO's work has produced two Declarations and 14 reports on bioethical topics. WHO focuses more on technical matters, using its scarce resources to respond to international health challenges, but it lacks experience in developing regulations and in discussing philosophy and bioethics from a multidisciplinary perspective.

Development of the UNESCO Declaration began in 2001 when the Director General asked the International Bioethics Committee (IBC) to prepare a report on bioethical issues, which, in 2003, became the basis for a larger project. The IBC was asked to develop a document that would set a worldwide standard for bioethics, based on human dignity, rights and freedoms in a multicultural context.

In January, 2004, the IBC sent questionnaires to 190 countries, receiving only 67 replies (including 31 from North America and Europe, 11 from Africa, and 6 from Latin America). The questionnaires were criticized for not providing a context and for being too superficial (Snead 2009), but the responses resulted in a meeting to decide the process for the preparation of a draft document. Representatives from many international agencies participated, including the World Health Organization, NGOs, and national ethics commissions. In April, 2004, at the end of the meeting, a committee was formed to develop the Declaration. The committee was given a tight work schedule, with seven meetings prior to the first draft of the document due in January, 2005.

The IBC issued the first outline of the proposed document in June, 2004, and shared it with the Intergovernmental Bioethics Committee (IGBC). IGBC members, especially Brazil, fiercely criticized the document for not being sufficiently ambitious and for not including a section on piracy of traditional medicine and the pharmaceutical knowledge of indigenous people. Other IGBC members (USA, Canada and Germany) criticized the binding character proposed for the Declaration. Between July, 2004, and January, 2005, the IBC met four times and asked for more input from the different countries, but received only 27 responses. The IBC and the IGBC met from January 24–28, 2005, to discuss the fourth draft. The IGBC members expressed similar objections to those of the previous June, and found important discrepancies in some subjects; for example, Holland had wanted to eliminate explicit phrases such as "respect for human life" which could be used against stem cell research or abortions, and the USA objected to phrases such as "access to health care services, including sexual and reproductive health", because of their possible interpretation as a defense of abortion rights. Two weeks after the meeting, the IBC issued the final draft, which ignored most of the suggestions of the IGBC (Snead 2009).

Two months later, negotiations began with the country representatives, who considered the draft to be inadequate and in need of important modifications. There were criticisms about the secrecy of the IBC, the questionnaire that had been distributed, and the composition of the IBC itself – for not having sufficient regional diversity, and for having too many human rights lawyers and too few bioethics experts. National differences surfaced during these discussions. The low- and middle-income countries, led by Brazil, asked to include issues of biopiracy, access to quality health services and essential medications, and protection of the biosphere. Germany, Japan, Canada, and the United States objected to the binding nature of the

Declaration, the breadth of the issues (which included many social problems), and threats to intellectual property rights. Other countries (United Kingdom, South Korea, Japan, and Holland) wanted to eliminate everything that could impede research with embryos and even proposed the use of the term person rather than human being, while the Vatican, United States, and Costa Rica insisted on respect for human dignity and the right to life. France, for its part, wanted the Declaration to be binding, and to be the first of a series of documents on bioethical issues.

In subsequent meetings, all references to "binding" clauses and virtually everything that had been written by the IBC were eliminated, and the differences between the viewpoints of high and low- and middle-income countries persisted. The United States shared with low- and middle-income countries – especially in Africa and Latin America – an interest in upholding respect for life and human dignity, while disagreeing about including social, political, and economic issues, such as an emphasis on illiteracy and a right to medications, within the concept of bioethics. The different positions were well defined, and appeared irreconcilable until the United States offered the possibility of including low- and middle-income country concerns in the language of the World Health Organization, without mentioning "bioethics", and changing the reference to sexual and reproductive health to "access to quality health services and essential medications, especially for the health of women and children." With this suggestion, the tone of the negotiations changed, and the Universal Declaration of Bioethics and Human Rights was adopted by acclamation at the UNESCO 33rd. General Conference, October 19, 2005 (Snead 2009).

While some defended the Declaration (Andorno 2007, 2009; Macklin 2005), others criticized it for being too vague and abstract (Faunce and Nasu 2009; Snead 2009; Trotter 2009), having internal contradictions (Selgelid 2005; Williams 2005), repeating what was already included in other documents (Macklin 2005; Bennett and Murray 2009), and for not having credibility among bioethicists (Williams 2005). Benatar (2005) pointed out that Declarations approved by consensus generally were vague and minimal, that is, they could be interpreted in many ways and ignored points where there was disagreement. Many felt it would have been preferable to utilize UNESCO's resources to study the principles on which to base a universal declaration of bioethics, take the necessary time to consult with member countries, reflect seriously on the information gathered, and improve implementation possibilities (Macpherson 2007). Others said that cultural differences had received too little attention, and that there had not been sufficient emphasis on the great inequality of access to power and the resources available to different countries, with the need to reduce these differences before the Declaration could be implemented (Rawlison and Dochin 2005). While recognizing that the document contains theoretical inconsistencies and practical limitations, Asai and Oe (2005) and Häyry and Takala (2005) think that the Declaration is useful because it promotes taking into account ethical ideas when discussing issues concerning human beings. It is certain that the Declaration has been the topic of much discussion between bioethicists and promoters of human rights.

2.8 The Declaration of Buenos Aires

The Declaration of Buenos Aires was approved during the General Assembly of the First Latin-American Workshop on Ethics and Clinical Trials, attended by 22 professionals from five countries (Argentina, Brazil, Costa Rica, Mexico, and Peru) held in Buenos Aires, Argentina, on May 13–15, 2008. One objective of the Workshop was to develop a research agenda, which would produce useful information to put pressure on, and eliminate ethical violations in clinical research conducted in Latin America. Workshop participants included social scientists, clinicians, community organizations, and bioethics specialists. A 20-point Declaration emerged from the workshop discussions, with the wording of each item based on the knowledge and observations of the workshop participants on how clinical trials are being implemented in Latin America. The Declaration of Buenos Aires is not a Code of Ethics, but a preliminary and incomplete assembly of ideas, to bring the ethical violations routinely occurring in Latin America to the attention of clinical trials sponsors, researchers, governmental authorities and the Courts. It is supported by 17 Latin American institutions (Ugalde and Homedes 2009).

2.9 Discussion

Of all the codes and/or declarations of ethics, not one is perfect. Several contain internal contraindications, and a comparison between the different documents reveals even more (Lie et al. 2004; Fischer 2006; Goodyear et al. 2007; Rid and Schmidt 2010; Gunson 2009). All have been compiled in response to ethical violations taking place during research with human subjects up to the present day. Some are very general, and can be interpreted in many ways; the most specific cannot be adopted by consensus, because they represent the opinions of the groups which were able to dominate the discussions at that time, as has occurred with the recent versions of the Declaration of Helsinki (Benatar 2005; Rid and Schmidt 2010).

Ethical problems during clinical trials are present in all parts of the world,[5] but tend to be greater in low- and middle-income countries where the regulatory agencies are weaker, where there is less ability to conduct a scientific-ethical evaluation of research projects, where there are fewer opportunities to carry out research independently from pharmaceutical industry financing, and where there are fewer groups able to monitor the implementation of clinical trials. The concerns and disagreements generated around the Declaration of Helsinki (1996 and 2000) led to the development of standards to govern clinical trials in low- and middle-income countries by the pharmaceutical industry (Bennett and Murray 2009), bioethicists (Benatar and Singer

[5] *The American Journal of Bioethics* published a series of articles on the weaknesses of the United States system in November, 2008 (Vol. 8, No. 11). Also Burris and Moss (2006), and Federman et al. (2002).

2000; Hutton 2000; Shapiro and Meslin 2001; Benatar 2002; David 2002; Participants 2002; Emanuel et al. 2004; Hyder et al. 2004; Wendler et al. 2004; Skene 2007), and various countries themselves. The report by the National Bioethics Advisory Commission (USA) (2001), the report by Nuffield Council on Bioethics (United Kingdom) (2002), and the 2003 report by the European Group on Ethics and Science and New Technologies (European Council and European Parliament 2001) brought into force by the Member states in 2004 offer their opinions on the ethical aspects of clinical research in low- and middle-income countries. In 2004, the Nuffield Council on Bioethics and the Medical Research Council of South Africa organized a conference, which produced another discussion document (Nuffield Council of Bioethics 2005). Not all these initiatives have been well received (see below).

When talking about ethical guidelines to govern clinical research in low- and middle-income countries, various issues should be part of the discussion, including: (1) imperialism, and moral universalism or relativism; (2) standard treatment in low- and middle-income countries and the concept of vulnerability; (3) risk-benefit balance; and (4) the ability to appropriately conduct clinical trials and ethical and scientific reviews.

2.9.1 Imperialism, and Moral Universalism or Relativism

Are the ethical principles, which govern research with humans the same everywhere in the world, or should they be adapted to the conditions in the country where the research takes place? If we look for the answer to this question in the ethical codes, they all clearly put the welfare of the individual before any scientific advances that may result from the study. From this, we can deduce that all human beings have the same rights, and that nobody should be exposed to risks for the benefit of science. However, when ethicists have to embed these principles in the specific reality of each project, the answer is not so clear. Some say that ethical principles are absolute, and therefore universal, although perhaps the way respect for those principles is expressed may vary according to local culture (Angell 1988; Shapiro and Meslin 2001; Kopelman 2005). For example, in many Latin American contexts, respecting the autonomy of the patient may require the involvement of his/her nuclear family when obtaining informed consent, especially if the patient is unaware of the diagnosis, which, for different reasons, is common when faced with cancer or another terminal illness. Love and Fost (1997) give a similar example when obtaining consent from mothers with breast cancer in Vietnam. At the other extreme are those who consider that ethical principles depend on the environment (Christakis et al. 1991). Their viewpoint is that studies with placebo control in low- and middle-income countries are justified, because none of the study participants would receive treatment if they were not enrolled in the clinical trial.

Another contemporary viewpoint is that northern countries, especially the USA, should not try to impose their ethical values on the rest of the world (Macklin 2001; Tealdi 2006; Garrafa and Lorenzo 2008). This view has been strengthened during

the last decade as a result of the controversy surrounding the revisions to the Declaration of Helsinki regarding the use of placebos and the need to provide access to the most effective treatment, at least to the study participants, and possibly (CIOMS and the Nuffield Council on Bioethics) to the whole community (Wolinsky 2006). The conflicts surrounding the Declaration of Helsinki have been seen as breaking the universal character of ethics in the declarations, codes, and ethical standards written before 1990. Obviously, when the FDA announced that studies conducted in other countries had to comply only with Good Clinical Practice, the debate became more antagonistic (Kimmelman et al. 2009).

Latin American bioethicists (Tealdi 2006; Garrafa and Lorenzo 2008) defend the need to develop a bioethics framework responsive to Latin American values, with an emphasis on increasing solidarity to decrease social inequity, one of the most serious problems of the region. Following the same line of thought, these authors say that the provision of courses in research bioethics by the Fogarty 6 International Center (NIH), USA, in response to a 2001 report from the National Bioethics Advisory Committee (2001) is one way to gain influence among Latin American ethicists, a form of moral imperialism which is not imposed by force, but rather by changing the culture.

Macklin (2001) recognized the frequent limitations of ethics committees in low- and middle-income countries, but also questioned the supposed superiority of the United States to dictate the application of ethical criteria in less developed nations. Approval of clinical trials through an ethics committee based in the USA – or another part of the world – does not guarantee that the clinical trial would be ethical. As a consultant to the UNAIDS program, she revised several protocols which had been approved by ethics committees in the USA for studies to be conducted in low- and middle-income countries, and verified that some ethics committees were not aware of the psychological risks of clinical trials, ignored issues of confidentiality, and/or approved informed consent materials with major shortcomings.

2.9.2 Standard Treatment in Low- and Middle-Income Countries, and the Concept of Vulnerability

In the world population, 13 % consume 87 % of medications, which, leads us to safely say that most residents of low- and middle-income countries lack access to needed medicines. Several ethicists have no objection to placebo controlled studies in these countries, because patients have no access to treatment anyway and the trials offer the possibility to advance science (Levine 1998, 1999). Others (Lurie and Wolfe 1997) argue that lack of access is an economic issue, which cannot justify studies in these populations that would not be permitted in industrialized countries. Some think that people who have limited access to medications qualify as vulnerable because participation in a study may be their only opportunity to receive treatment (see Chap. 3). It is at least probable that this population, with probably low levels of education and income, has more difficulty in understanding

that they are participating in a study, and will assume risks without any guarantee of therapeutic benefit. If the person offering the possibility of participating in a clinical trial is the patient's public sector physician, patient autonomy is further limited. Low income residents in Latin America respect physicians and accept medical recommendations without question. Consent to participate may be given because people feel pressured and fear reprisals, such as problems with access to future care. In these circumstances it is important to do whatever possible to respect the autonomy of patients (and/or their families or legal representatives), and to ensure that potential study participants understand what the study will, and will not, accomplish, together with its related risks and benefits.

Other ethicists express a distinct opinion, saying that the treatment offered to study participants in low- and middle-income countries does not always have to be the best available worldwide, because the provision of treatment not normally available could delay the advancement of therapeutics in the countries where the study takes place (London 2000; Koski and Nightingale 2001; Killen et al. 2002; Zumla and Costello 2002; Wendler et al. 2004). Lie et al. (2004) studied the various ethical guidelines for low- and middle-income countries, and concluded that they all allow the implementation of clinical trials in low- and middle-income countries that do not offer participants in the control group the best available treatment in the world for the pathology studied. Although each document had a slightly different emphasis, all used basically the same criteria to justify the use of a lesser treatment than that available on an international level: (1) there is a valid scientific reason to offer that particular treatment to the control group; (2) the clinical trial must provide sufficient benefits to the population involved in the study, and (3) there must be an acceptable risk/benefit balance for each one of the study participants (see Table 2.1). According to this perspective, all these documents, which with the exceptions of CIOMS (2002) and UNAIDS (2000) for the most part had been written by various groups of experts in industrialized countries during the decade between 2000 and 2009, did not include as a moral absolute the provision of the best internationally available treatment for the control group.

2.9.3 The Balance of Risks and Benefits

All ethical guidelines say that no treatment or intervention can be withheld from clinical trial participants who can benefit from them and they would receive if they were not participating in biomedical research (Lie et al. 2004). Controversial issues are: (1) whether clinical trials conducted in low- and middle-income countries should respond to the health priorities of the country; and (2) what are the "reasonable" benefits to be provided to clinical trial participants and their communities if the study intervention is shown to be effective, and at what price and for how long should treatment be provided (Fair benefits 2002).

Some think that clinical trials could take place in low- and middle-income countries whenever some residents are affected by the disease studied, even if it

Table 2.1 Ethical Guidelines for Human Research in Low- and middle-income Countries and Acceptable Therapies for the Control Group

Organization	Scientific validity	Social benefits for the country	Risk//benefit ratio for the volunteer
UNAIDS	Acceptable scientific protocol	Plans to ensure availability must be defined during the initial phases of vaccine development	As a minimum, there must be guarantees of the best health service available in the country
National Bioethics Advisory Committee (2001)	There must be justification of the choice of study design	Explanation of how an effective study medication will be made available to the residents of the country where the study took place	The ethics committee must assess the risk to participants
CIOMS (2002)	The study would not yield reliable scientific information if the available treatment was to be provided	The clinical trial should relate to the needs of the participating population, and assure "reasonable" access to the treatment which has been shown to be effective	There is a balance between risks and potential benefits, with a minimization of risks for participants in clinical trials
European Group on Ethics etc. (2001)	The method meets the objectives of the study, and there is no other alternative methodology	One possible justification is to simplify or reduce the cost of treatment in the country where research is conducted	Special attention must be paid to the risk/benefit balance at the individual level
Nuffield Council (2002, 2005)	The research design must meet the research objective	Consideration must be given to the sustainability and affordability of the treatment selected	As a minimum, the selected treatment should be available at the national level

Source: Lie et al. (2004)

is not a government priority, and they say that if the study complies with both ethical principles and the regulations of the host country, the researchers have no further obligation to the study participants (Macklin 2001). Others feel that if there is no intent to improve access to a proven treatment for study participants and their communities, there is a violation of the principle of distributive justice, and the study should be rejected (Page 2000; Crouch and Arras 1998; Glantz et al. 1998). Benatar and Singer (2000) go to the root of the problem, asserting that the need to eliminate social injustice and inequality between nations requires clinical trials to benefit the places where they are carried out, and that ways must be found to turn new discoveries into accessible therapies for the study community.

2.9.4 *The Ability to Conduct Clinical Trials and Ethical Reviews*

There is some concern about the ability of low- and middle-income countries to conduct scientific and ethical evaluations of clinical trials. There have been suggestions that research should not take place in countries that do not have the capacity to protect their residents, but other experts think that this is an extreme position and have suggested ways to overcome the problem. The CIOMS document (2002) and the article by Hyder et al. (2004) are interesting because they recognize the weaknesses of low- and middle-income countries and ask for protocols to be approved also by an ethics committee in the country of the sponsor. The National Bioethics Advisory Committee (2001) and the Nuffield (2002) reports support the exportation of the ethical review model to low- and middle-income countries and promote the development of resources in countries where research is conducted. Some authors see this as moral imperialism (Tealdi 2006; Garrafa and Lorenzo 2008; Lescano et al. 2008; McIntosh et al. 2008). One initiative has been to establish agreements between universities in high income countries and those in low- and middle-income countries to improve the skills needed to conduct clinical trials (Sidle et al. 2006).

From our perspective, and as can be seen throughout this book, there is little doubt that the systems for ethical and scientific review of studies with human subjects must be improved, especially in low- and middle-income countries.

2.10 Conclusion

The improvement of ethical codes governing clinical trials is a constant concern for bioethicists, but, even if the codes achieve perfection, their application is a different matter. In most cases, the problems are basic violations of human rights. Latin America needs to establish monitoring systems for each stage of clinical trial implementation; the reviews currently conducted by some regulatory agencies during the process of deciding whether or not to market a product are not enough.

But however sophisticated the monitoring systems may be, real change will occur only when the culture of those who sponsor and conduct research with human subjects will have internalized ethical and scientific principles, and will express increasing respect for both the research process and the rights of the study participants. Governments, universities, and professional associations could take the lead in this by developing legislation and systems supportive of the principles of the desired culture.

Finally, if clinical trials in low- and middle-income countries continue, ways must be found so that all residents in these countries can access necessary medications. Without this provision, we condone the violation of the principle of justice, exploiting the vulnerability of those who cannot receive treatment unless they participate in clinical trials.

Appendix A: A Review and Critique of International Ethical Principles: Annexes

THE NÜREMBURG CODE. (Nüremberg International Tribunal) 1947

Reprinted from *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Vol. 2, pp. 181–182*. Washington, DC: U. S. Government Printing Office, 1949. (http://ohsr.od.nih.gov/guidelines/nuremberg.html)

Directives for Human Experimentation

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

   The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility, which may not be delegated to another with impunity.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. Introduction

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. Principles for All Medical Research

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study

when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. Additional Principles for Medical Research Combined with Medical Care

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

http://www.wma.net/en/30publications/10policies/b3/17c.pdf

Universal Declaration on Bioethics and Human Rights

Adopted by acclamation on 19 October 2005 by the 33rd session of the General Conference of UNESCO.

The General Conference

Conscious of the unique capacity of human beings to reflect upon their own existence and on their environment, to perceive injustice, to avoid danger, to assume responsibility, to seek cooperation and to exhibit the moral sense that gives expression to ethical principles,

Reflecting on the rapid developments in science and technology, which increasingly affect our understanding of life and life itself, resulting in a strong demand for a global response to the ethical implications of such developments,

Recognizing that ethical issues raised by the rapid advances in science and their technological applications should be examined with due respect to the dignity of the human person and universal respect for, and observance of, human rights and fundamental freedoms,

Resolving that it is necessary and timely for the international community to state universal principles that will provide a foundation for humanity's response to the ever-increasing dilemmas and controversies that science and technology present for humankind and for the environment,

Recalling the Universal Declaration of Human Rights of 10 December 1948, the Universal Declaration on the Human Genome and Human Rights adopted by the General Conference of UNESCO on 11 November 1997 and the International Declaration on Human Genetic Data adopted by the General Conference of UNESCO on 16 October 2003,

Noting the United Nations International Covenant on Economic, Social and Cultural Rights and the International Covenant on Civil and Political Rights of 16 December 1966, the United Nations International Convention on the Elimination of All Forms of Racial Discrimination of 21 December 1965, the United Nations Convention on the Elimination of All Forms of Discrimination against Women of 18 December 1979, the United Nations Convention on the Rights of the Child of 20 November 1989, the United Nations Convention on Biological Diversity of 5 June 1992, the Standard Rules on the Equalization of Opportunities for Persons with Disabilities adopted by the General Assembly of the United Nations in 1993, the UNESCO Recommendation on the Status of Scientific Researchers of 20 November 1974, the UNESCO Declaration on Race and Racial Prejudice of 27 November 1978, the UNESCO Declaration on the Responsibilities of the Present Generations Towards Future Generations of 12 November 1997, the UNESCO Universal Declaration on Cultural Diversity of 2 November 2001, the ILO Convention 169 concerning Indigenous and Tribal Peoples in Independent Countries of 27 June 1989, the International Treaty on Plant Genetic Resources for Food and Agriculture which was adopted by the FAO Conference on 3 November 2001 and entered into force on 29 June 2004, the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) annexed to the Marrakech Agreement establishing the World Trade Organization, which entered into force on 1 January 1995, the Doha Declaration on the TRIPS Agreement and Public Health of 14 November 2001 and other relevant international instruments adopted by the United Nations and the specialized agencies of the United Nations system, in particular the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO),

Also noting international and regional instruments in the field of bioethics, including the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine of the Council of Europe, which was adopted in 1997 and entered into force in 1999, together with its Additional Protocols, as well as national legislation and regulations in the field of bioethics and the international and regional codes of conduct and guidelines and other texts in the field of bioethics, such as the Declaration of Helsinki of the World Medical Association on Ethical Principles for Medical Research Involving Human Subjects, adopted in 1964 and amended in 1975, 1983, 1989, 1996 and 2000 and the International Ethical Guidelines for Biomedical Research Involving Human Subjects of the Council for International Organizations of Medical Sciences, adopted in 1982 and amended in 1993 and 2002,

Recognizing that this Declaration is to be understood in a manner consistent with domestic and international law in conformity with human rights law,

Recalling the Constitution of UNESCO adopted on 16 November 1945,

Considering UNESCO's role in identifying universal principles based on shared ethical values to guide scientific and technological development and social transformation in order to identify emerging challenges in science

and technology taking into account the responsibility of the present generations towards future generations, and that questions of bioethics, which necessarily have an international dimension, should be treated as a whole, drawing on the principles already stated in the Universal Declaration on the Human Genome and Human Rights and the International Declaration on Human Genetic Data and taking account not only of the current scientific context but also of future developments,

Aware that human beings are an integral part of the biosphere, with an important role in protecting one another and other forms of life, in particular animals,

Recognizing that, based on the freedom of science and research, scientific and technological developments have been, and can be, of great benefit to humankind in increasing, *inter alia*, life expectancy and improving the quality of life, and *emphasizing* that such developments should always seek to promote the welfare of individuals, families, groups or communities and humankind as a whole in the recognition of the dignity of the human person and universal respect for, and observance of, human rights and fundamental freedoms,

Recognizing that health does not depend solely on scientific and technological research developments but also on psychosocial and cultural factors,

Also recognizing that decisions regarding ethical issues in medicine, life sciences and associated technologies may have an impact on individuals, families, groups or communities and humankind as a whole,

Bearing in mind that cultural diversity, as a source of exchange, innovation and creativity, is necessary to humankind and, in this sense, is the common heritage of humanity, but *emphasizing* that it may not be invoked at the expense of human rights and fundamental freedoms,

Also bearing in mind that a person's identity includes biological, psychological, social, cultural and spiritual dimensions,

Recognizing that unethical scientific and technological conduct has had a particular impact on indigenous and local communities,

Convinced that moral sensitivity and ethical reflection should be an integral part of the process of scientific and technological developments and that bioethics should play a predominant role in the choices that need to be made concerning issues arising from such developments,

Considering the desirability of developing new approaches to social responsibility to ensure that progress in science and technology contributes to justice, equity and to the interest of humanity,

Recognizing that an important way to evaluate social realities and achieve equity is to pay attention to the position of women,

Stressing the need to reinforce international cooperation in the field of bioethics, taking into account, in particular, the special needs of developing countries, indigenous communities and vulnerable populations,

Considering that all human beings, without distinction, should benefit from the same high ethical standards in medicine and life science research,

Proclaims the principles that follow and *adopts* the present Declaration.

General Provisions

Article 1 – Scope

1. This Declaration addresses ethical issues related to medicine, life sciences and associated technologies as applied to human beings, taking into account their social, legal and environmental dimensions.
2. This Declaration is addressed to States. As appropriate and relevant, it also provides guidance to decisions or practices of individuals, groups, communities, institutions and corporations, public and private.

Article 2 – Aims
The aims of this Declaration are:

(a) to provide a universal framework of principles and procedures to guide States in the formulation of their legislation, policies or other instruments in the field of bioethics;
(b) to guide the actions of individuals, groups, communities, institutions and corporations, public and private;
(c) to promote respect for human dignity and protect human rights, by ensuring respect for the life of human beings, and fundamental freedoms, consistent with international human rights law;
(d) to recognize the importance of freedom of scientific research and the benefits derived from scientific and technological developments, while stressing the need for such research and developments to occur within the framework of ethical principles set out in this Declaration and to respect human dignity, human rights and fundamental freedoms;
(e) to foster multidisciplinary and pluralistic dialogue about bioethical issues between all stakeholders and within society as a whole;
(f) to promote equitable access to medical, scientific and technological developments as well as the greatest possible flow and the rapid sharing of knowledge concerning those developments and the sharing of benefits, with particular attention to the needs of developing countries;
(g) to safeguard and promote the interests of the present and future generations;
(h) to underline the importance of biodiversity and its conservation as a common concern of humankind.

Principles

Within the scope of this Declaration, in decisions or practices taken or carried out by those to whom it is addressed, the following principles are to be respected.

Article 3 – human dignity and human rights

1. Human dignity, human rights and fundamental freedoms are to be fully respected.

2. The interests and welfare of the individual should have priority over the sole interest of science or society.

Article 4 – Benefit and harm
In applying and advancing scientific knowledge, medical practice and associated technologies, direct and indirect benefits to patients, research participants and other affected individuals should be maximized and any possible harm to such individuals should be minimized.

Article 5 – Autonomy and individual responsibility
The autonomy of persons to make decisions, while taking responsibility for those decisions and respecting the autonomy of others, is to be respected. For persons who are not capable of exercising autonomy, special measures are to be taken to protect their rights and interests.

Article 6 – Consent

1. Any preventive, diagnostic and therapeutic medical intervention is only to be carried out with the prior, free and informed consent of the person concerned, based on adequate information. The consent should, where appropriate, be express and may be withdrawn by the person concerned at any time and for any reason without disadvantage or prejudice.
2. Scientific research should only be carried out with the prior, free, express and informed consent of the person concerned. The information should be adequate, provided in a comprehensible form and should include modalities for withdrawal of consent. Consent may be withdrawn by the person concerned at any time and for any reason without any disadvantage or prejudice. Exceptions to this principle should be made only in accordance with ethical and legal standards adopted by States, consistent with the principles and provisions set out in this Declaration, in particular in Article 27, and international human rights law.
3. In appropriate cases of research carried out on a group of persons or a community, additional agreement of the legal representatives of the group or community concerned may be sought. In no case should a collective community agreement or the consent of a community leader or other authority substitute for an individual's informed consent.

Article 7 – Persons without the capacity to consent
In accordance with domestic law, special protection is to be given to persons who do not have the capacity to consent:

(a) authorization for research and medical practice should be obtained in accordance with the best interest of the person concerned and in accordance with domestic law. However, the person concerned should be involved to the greatest extent possible in the decision-making process of consent, as well as that of withdrawing consent;

(b) research should only be carried out for his or her direct health benefit, subject to the authorization and the protective conditions prescribed by law, and if there is no research alternative of comparable effectiveness with research participants able to consent. Research which does not have potential direct health benefit should only be undertaken by way of exception, with the utmost restraint, exposing the person only to a minimal risk and minimal burden and if the research is expected to contribute to the health benefit of other persons in the same category, subject to the conditions prescribed by law and compatible with the protection of the individual's human rights. Refusal of such persons to take part in research should be respected.

Article 8 – Respect for human vulnerability and personal integrity
In applying and advancing scientific knowledge, medical practice and associated technologies, human vulnerability should be taken into account. Individuals and groups of special vulnerability should be protected and the personal integrity of such individuals respected.

Article 9 – Privacy and confidentiality
The privacy of the persons concerned and the confidentiality of their personal information should be respected. To the greatest extent possible, such information should not be used or disclosed for purposes other than those for which it was collected or consented to, consistent with international law, in particular international human rights law.

Article 10 – Equality, justice and equity
The fundamental equality of all human beings in dignity and rights is to be respected so that they are treated justly and equitably.

Article 11 – Non-discrimination and non-stigmatization
No individual or group should be discriminated against or stigmatized on any grounds, in violation of human dignity, human rights and fundamental freedoms.

Article 12 – Respect for cultural diversity and pluralism
The importance of cultural diversity and pluralism should be given due regard. However, such considerations are not to be invoked to infringe upon human dignity, human rights and fundamental freedoms, nor upon the principles set out in this Declaration, nor to limit their scope.

Article 13 – Solidarity and cooperation
Solidarity among human beings and international cooperation towards that end are to be encouraged.

Article 14 – Social responsibility and health

1. The promotion of health and social development for their people is a central purpose of governments that all sectors of society share.

2. Taking into account that the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition, progress in science and technology should advance:

   (a) access to quality health care and essential medicines, especially for the health of women and children, because health is essential to life itself and must be considered to be a social and human good;
   (b) access to adequate nutrition and water;
   (c) improvement of living conditions and the environment;
   (d) elimination of the marginalization and the exclusion of persons on the basis of any grounds;
   (e) reduction of poverty and illiteracy.

Article 15 – Sharing of benefits

1. Benefits resulting from any scientific research and its applications should be shared with society as a whole and within the international community, in particular with developing countries. In giving effect to this principle, benefits may take any of the following forms:

   (a) special and sustainable assistance to, and acknowledgement of, the persons and groups that have taken part in the research;
   (b) access to quality health care;
   (c) provision of new diagnostic and therapeutic modalities or products stemming from research;
   (d) support for health services;
   (e) access to scientific and technological knowledge;
   (f) capacity-building facilities for research purposes;
   (g) other forms of benefit consistent with the principles set out in this Declaration.

2. Benefits should not constitute improper inducements to participate in research.

Article 16 – Protecting future generations
The impact of life sciences on future generations, including on their genetic constitution, should be given due regard.

Article 17 – Protection of the environment, the biosphere and biodiversity
Due regard is to be given to the interconnection between human beings and other forms of life, to the importance of appropriate access and utilization of biological and genetic resources, to respect for traditional knowledge and to the role of human beings in the protection of the environment, the biosphere and biodiversity.

Application of the Principles

Article 18 – Decision-making and addressing bioethical issues

1. Professionalism, honesty, integrity and transparency in decision-making should be promoted, in particular declarations of all conflicts of interest and appropriate sharing of knowledge. Every endeavour should be made to use the best available scientific knowledge and methodology in addressing and periodically reviewing bioethical issues.
2. Persons and professionals concerned and society as a whole should be engaged in dialogue on a regular basis.
3. Opportunities for informed pluralistic public debate, seeking the expression of all relevant opinions, should be promoted.

Article 19 – Ethics committees

Independent, multidisciplinary and pluralist ethics committees should be established, promoted and supported at the appropriate level in order to:

(a) assess the relevant ethical, legal, scientific and social issues related to research projects involving human beings;
(b) provide advice on ethical problems in clinical settings;
(c) assess scientific and technological developments, formulate recommendations and contribute to the preparation of guidelines on issues within the scope of this Declaration;
(d) foster debate, education and public awareness of, and engagement in, bioethics.

Article 20 – Risk assessment and management

Appropriate assessment and adequate management of risk related to medicine, life sciences and associated technologies should be promoted.

Article 21 – Transnational practices

1. States, public and private institutions, and professionals associated with transnational activities should endeavour to ensure that any activity within the scope of this Declaration, undertaken, funded or otherwise pursued in whole or in part in different States, is consistent with the principles set out in this Declaration.
2. When research is undertaken or otherwise pursued in one or more States (the host State(s)) and funded by a source in another State, such research should be the object of an appropriate level of ethical review in the host State(s) and the State in which the funder is located. This review should be based on ethical and legal standards that are consistent with the principles set out in this Declaration.
3. Transnational health research should be responsive to the needs of host countries, and the importance of research contributing to the alleviation of urgent global health problems should be recognized.

4. When negotiating a research agreement, terms for collaboration and agreement on the benefits of research should be established with equal participation by those party to the negotiation.
5. States should take appropriate measures, both at the national and international levels, to combat bioterrorism and illicit traffic in organs, tissues, samples, genetic resources and genetic related materials.

Promotion of the Declaration

Article 22 – Role of states

1. States should take all appropriate measures, whether of a legislative, administrative or other character, to give effect to the principles set out in this Declaration in accordance with international human rights law. Such measures should be supported by action in the spheres of education, training and public information.
2. States should encourage the establishment of independent, multidisciplinary and pluralist ethics committees, as set out in Article 19.

Article 23 – Bioethics education, training and information

1. In order to promote the principles set out in this Declaration and to achieve a better understanding of the ethical implications of scientific and technological developments, in particular for young people, States should endeavour to foster bioethics education and training at all levels as well as to encourage information and knowledge dissemination programmes about bioethics.
2. States should encourage the participation of international and regional intergovernmental organizations and international, regional and national non-governmental organizations in this endeavour.

Article 24 – International cooperation

1. States should foster international dissemination of scientific information and encourage the free flow and sharing of scientific and technological knowledge.
2. Within the framework of international cooperation, States should promote cultural and scientific cooperation and enter into bilateral and multilateral agreements enabling developing countries to build up their capacity to participate in generating and sharing scientific knowledge, the related know-how and the benefits thereof.
3. States should respect and promote solidarity between and among States, as well as individuals, families, groups and communities, with special regard for those rendered vulnerable by disease or disability or other personal, societal or environmental conditions and those with the most limited resources.

Article 25 – Follow-up action by UNESCO

1. UNESCO shall promote and disseminate the principles set out in this Declaration. In doing so, UNESCO should seek the help and assistance of the

Intergovernmental Bioethics Committee (IGBC) and the International Bioethics Committee (IBC).
2. UNESCO shall reaffirm its commitment to dealing with bioethics and to promoting collaboration between IGBC and IBC.

Final Provisions

Article 26 – Interrelation and complementarity of the principles
This Declaration is to be understood as a whole and the principles are to be understood as complementary and interrelated. Each principle is to be considered in the context of the other principles, as appropriate and relevant in the circumstances.

Article 27 – Limitations on the application of the principles
If the application of the principles of this Declaration is to be limited, it should be by law, including laws in the interests of public safety, for the investigation, detection and prosecution of criminal offences, for the protection of public health or for the protection of the rights and freedoms of others. Any such law needs to be consistent with international human rights law.

Article 28 – Denial of acts contrary to human rights, fundamental freedoms and human dignity
Nothing in this Declaration may be interpreted as implying for any State, group or person any claim to engage in any activity or to perform any act contrary to human rights, fundamental freedoms and human dignity.

http://www.bioethics.gov.cy/Law/cnbc/cnbc.nsf/All/20367BA1ED3D0F34C2257292002AEF74/$file/Universal%20Declaration%20on%20Bioethics%20and%20Human%20Rights_EN.pdf

The Buenos Aires Declaration on Ethics and Clinical Trials

"The Buenos Aires Declaration on Ethics and Clinical Trials" was unanimously approved at the First Latin American Workshop on Ethics and Clinical Trials and endorsed by the Latin American organizations that are listed at the end of the Declaration.

Both the Workshop and the Declaration were a response to the rapidly increasing number of clinical trials that are taking place in the region and to the questions being raised as a result of the many alleged violations of ethics during the approval and implementation of the trials.

The Workshop was organized by the non-profit organization Salud y Fármacos (http://www.boletinfarmacos.org), incorporated both in the USA and Argentina, which also publishes the free-access electronic bulletin Boletín Fármacos. The Dutch Foundation WEMOS, the Health Science Center of the University of Texas and the Pan American Health Organization-Argentine also provided financial assistance for the workshop.

Salud y Fármacos and WEMOS perceive serious ethical flaws in the conditions surrounding clinical trials in Latin America and believe that the international health community should be aware of the situation.

The Declaration

At the General Assembly of the First Latin-American Workshop on Ethics and Clinical Trials (Buenos Aires, May 12 and 13, 2008) participants unanimously approved the following declaration:

1. Clinical trials can only be carried out if the population where the trials take place can benefit from their results.
2. Authorities of countries where clinical trials take place should require studies to strictly adhere to the "Universal Declaration of Bioethics and Human Rights" (UNESCO 2005).
3. All clinical trials that take place in Latin America must be registered with the national drug agency of the country where the trials take place or with the appropriate authority created for this purpose. The key information of the protocols should be made electronically available to the public.
4. In Latin America, protocols originating from outside the region must be translated by regionally-competent, expert translators for presentation to local authorities (the regulatory agencies, ethics committees, etc.) into the language of the country where the clinical trial takes place (Spanish, Portuguese, or French).
5. The informed consent should fulfill the following requirements:
   (a) Informed consent forms originating from outside the region must be translated by regionally-competent, expert translators.
   (b) Persons, totally independent from the clinical trial participants from all social and ethnic strata clearly understand the content of the informed consent form.
   (c) When indigenous populations participate in the trial, the informed consent form should be presented to them in their native language.
6. The ethics committees that approve the implementation of a clinical trial must be active in the supervision and monitoring of all critical steps, including recruiting of participants, data gathering and publication of results. The tasks should be specified in writing at the time the ethics committee approves the trial.
7. National health authorities should create a national registry of approved ethical committees, of research centers that have proven to have the technical competence to carry out clinical trials, and of researchers of known qualifications and honesty.
8. New drugs to be tested in clinical trials should be tested against the best available preventive, diagnostic and therapeutic methods. Placebos can be

used only when no other therapeutic procedure exists, or under exceptional, qualified circumstances, when this method is indispensable.

9. The results and findings of all the clinical trials should be communicated within a reasonable time to those who participated in the trials, and should be made available electronically to the public through the national drug agencies of the countries where the trials took place.
10. We condemn those clinical trials whose main objectives include the promotion of the commercialization of the tested drug.
11. In order to obtain authorization for a clinical trial, the pharmaceutical industry must commit itself to make the product economically accessible to those who need it in the country where the clinical trial took place if the drug tested is useful for the treatment of a disease.
12. It is necessary to initiate as soon as possible multi-centric studies of Contract Research Organizations (CROs) are operating in Latin America. The research should document the financial benefits obtained from the trials, their business history, and any complaints raised against them. Regulatory agencies should publish electronically the results of these studies to allow other countries to know the qualifications of the firms.
13. Following the initiative of the leading professional health journals in United States and the European Union, Latin American medical journals should not publish any results of clinical trials unless their protocols have been electronically posted before the initiation of the trial. Similarly, articles should not be published unless the authors declare possible conflicts of interest.
14. All benefits that clinical trial researchers obtain from trials should be made public. The information must be specific regarding the amount that researchers receive per participant recruited, and per participant that completes the trial. This information should be shared with trial participants as part of the informed consent. Other fringe benefits that the investigator receives from the industry should also be specified.
15. All persons who participate in clinical trials should be insured for potential risks they may suffer during the course of, or as a result of, the trial. The insurance policy should be paid by the pharmaceutical firm, CRO or organization that carries out the trial. The policies should be issued by reputable national or foreign insurance companies, and the damage payment should be equivalent to the amount that a person suffering a similar injury would receive in the country where the pharmaceutical firm responsible for the trial is headquartered.
16. As soon as it is discovered that a person appears as the author of an article on the results of a clinical trial that in fact was written by somebody else paid by a pharmaceutical industry or that his/her participation was minimal, the academic center to which the author is affiliated should start proceedings leading to an adequate sanction. If the author is a member of a CRO, the firm should be sanctioned and not be allowed to carry out additional clinical trials in the country.
17. We believe that clinical trials should be carried out by nonprofit organizations such as universities on their own or in collaboration with the ministry of health. The participation of nonprofit organizations should be promoted.

18. Every effort should be made to insure that those in the lowest income group and other vulnerable groups do not participate in clinical trials, unless they directly benefit from their findings.
19. The goal of a clinical trial is not to create wealth for an enterprise, organization or individual. Clinical trials can only take place to improve or augment the available therapeutic arsenal for the benefit of mankind.
20. There is a need to establish procedures to protect the blood and tissue samples obtained from clinical trial participants in order to preclude future abuses related to patent protection and the for-profit commercialization of derivatives of such samples.

Buenos Aires, May 13, 2008

The Declaration of Buenos Aires was written by the following: Dr. Jose Rubén Alcântara Bofim, Dr Patricia Andreotti, Dr. Corina Bontempo Duca de Freitas, Dr. Martín Cañas, Dr. Hernán Collado, Dr. Elisa Dibarbora, Ms. Susie Dutra, Dr. José Miguel Esquivel, Dr. Duilio Fuentes, Dr. Carmen Lidia Guerrero, Dr Núria Homedes, Dr. Gabriela Minaya, Ms. Susy Olave, Ms. Jimena Orchuela, Dr. Agustin Páez, Dr Analia Perez, Dr. Mario Salinas, Mr. Jacob Sijtsma, Dr. Juan Carlos Tealdi, Dr. Antonio Ugalde, Dra. Edith Valdez, Dra. Emma Verastegui, Dr. Susana Vidal.

The Declaration has been endorsed by the following organizations:

Acción Internacional para la Salud-Coordination Center for Latin America (AIS-LAC)

Roberto López Linares – Coordinator

Acción Internacional para la Salud-Bolivia (AIS-Bolivia)

Óscar Lanza MD – Coordinator

Acción Internacional para la Salud-Nicaragua (AIS-Nicaragua)

Leonel Arguello, MD -President

Asociacion Mexicana para el Uso Racional de los Medicamentos,

A.C. Rogelio Fernández MD – President

Cátedra de Derechos Humanos de la Facultad de Medicina de la Universidad de Buenos Aires

Claudio Capuano MD – Director

Cátedra Unesco de Bioética de la Universidad Nacional de Brasilia

Prof. Volnei Garrafa -Coordinator

Centro de Información de Medicamentos de la Universidad de Colombia (CIMUN)

José, Julián López QF – Coordinator General

Centro Universitario de Farmacología, Facultad de Ciencias Médicas, Universidad Nacional de La Plata (CUFAR) (Argentina) – Centro Colaborador OPS/OMS

Perla Mordujovich de Buschiazzo MD – Director

Comité de Defensa de los Derechos del Consumidor- Bolivia (CODECO)

Rodrigo Urquieta Arias – Coordinador

Drug Utilization Research Group, Latinoamérica (DURG-LA)

Claudia Vacca QF – President

Fundación Instituto para la Investigación del Medicamento en los Sistemas de Salud, Colombia (IFARMA)

Francisco Rossi MD- Director

Grupo Argentino para el Uso Racional del Medicamento (GAPURMED)

Luis Castiglioni MD – President

International Health Central American Institute Foundation (IHCAI FOUNDATION)

Dr. Mario Tristan, Director-General

Red Latinoamericana de Ética y Medicamentos RELEM (The Latin American Network of Ethics and Medicines)

Núria Homedes MD, DrPH – Coordinator

Red Latinoamericana y del Caribe de Bioética de UNESCO-Redbioética

Volnei Garrafa, DDS, PHD – President of Council of Directors

Salud y Fármacos

Antonio Ugalde, PhD – President, USA
Martín Cañás MD – President, Argentina

Sociedade Brasileira de Vigilancia de Medicamentos (Sobravime)

Jose Rubén Alcántara Bofim MD – President

http://www.saludyfarmacos.org/wp-content/files/Buenos_Aires_Declaration_on_Ethics_and_clinical_Trialsfinal.pdf

References

Andorno, R. 2002. Biomedicine and international human rights law: In search of a global consensus. *Bulletin of the World Health Organization* 80: 959–963.

Andorno, R. 2007. Global bioethics at UNESCO: In defense of the Universal Declaration of Bioethics and Human Rights. *Journal of Medical Ethics* 33: 150–154.

Andorno, R. 2009. Human dignity and human rights as a common ground for a global bioethics. *The Journal of Medicine and Philosophy* 34: 223–240.

Angell, M. 1988. Ethical imperialism? Ethics in international collaborative clinical research. *New England Journal of Medicine* 319: 1081–1083.

Asai, A., and S. Oe. 2005. A valuable up-to-date compendium of bioethical knowledge. *Developing World Bioethics* 5(3): 216–219.

Beecher, H.K. 1966. Ethics in clinical research. *New England Journal of Medicine* 274: 1354–1360.

Benatar, S.R. 1998. Imperialism, research ethics and global health. *Journal of Medical Ethics* 24: 221–222.

Benatar, S.R. 2002. Reflections and recommendations on research ethics in developing countries. *Social Science & Medicine* 54: 1131–1141.

Benatar, D. 2005. The trouble with universal declarations. *Developing World Bioethics* 5(3): 220–224.

Benatar, S.R., and P. Singer. 2000. A new look at international research ethics. *British Medical Journal* 321: 824–826.

Brandt, A.M. 1978. Racism and research: The case of the Tuskegee Syphilis Study. *The Hastings Center Report* 8(6): 21–29.

Brennan, T.A. 1999. Proposed revisions to the Declaration of Helsinki – Will they weaken the ethical principles underlying human research? *New England Journal of Medicine* 341(24): 1852–1853.

Burris, S., and K. Moss. 2006. US health researchers review their ethics review boards: A qualitative study. *Journal of Empirical Research on Human Research* 1(2): 39–58.

Christakis, N.A., L.A. Lynn, and A. Castelo. 1991. Clinical AIDS research that evaluates cost-effectiveness in the developing world. *IRB Review Human Subjects Research* 3: 6–8.

Conselho Federal de Medicina. 2008. Resolução CMF 1885/2008m Oct 22.

Council for International Organizations of Medical Sciences (CIOMS) and World Health Organization (WHO). 2002. International ethical guidelines for biomedical research involving. Human subjects. Geneva: CIOMS. http://www.fhi360.org/training/fr/retc/pdf_files/cioms.pdf. Accessed 21 Oct 2012.

Crouch, R.A., and J.D. Arras. 1998. AZT trials and tribulations. *The Hastings Center Report* 28(6): 26–34.

David, T.J. 2002. Ethics of healthcare research in developing countries. *Journal of the Royal Society of Medicine* 95(4): 275–279.

Dawson, A., and E. Garrard. 2006. In defense of moral imperialism: Four equal and universal prima facie principles. *Journal of Medical Ethics* 32: 200–204.

de Abajo, F.J. 2001. La Declaración de Helsinki VI: una revisión necesaria, pero ¿suficiente? (The declaration of Helskini VI: A necessary review, but is it sufficient?). *Revista Espanola de Salud Publica* 75: 407–420.

Department of Health and Human Services (DHHS-FDA). 2008. Human subject protection; Foreign clinical studies not conducted under an investigational new drug application: Final rule. *Federal Register* 73(82): 22800–22816.

Emanuel, E.J., R.A. Crouch, J.D. Arras, et al. 2003. Ethical and regulatory guidance for research with humans. In *Ethical and regulatory aspects of clinical research*, ed. E.J. Emanuel, R.A. Crouch, J.D. Arras, et al., 25–94. Baltimore: The Johns Hopkins University Press.

Emanuel, E.J., D. Wendler, J. Killen, and C. Grady. 2004. What makes clinical research in developing countries ethical? The benchmarks of ethical research. *Journal of Infectious Diseases* 189: 930–937.

EMEA. 2001. EMEA/CPMP position statement on the use of placebo in clinical trials with regard to the revised declaration of Helsinki 17424/01. London, 28 June. Cited in Klimovsky et al. (2002).

European Council and European Parliament. 2001. Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative

provisions of the member States relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. April. http://europa.eu.int/eur-lex/pri/en/oj/dat/2001/l_12120010501en00340044.pdf. Accessed 1 Nov 2012.

Faden, R.R., S.E. Lederer, and J.D. Moreno. 1996. US medical researchers, the Nuremberg Doctors trial, and the Nuremberg code: A review of findings of the Advisory Committee on Human Radiation Experiments. *JAMA: The Journal of the American Medical Association* 276: 1667–1671.

Fair benefits for research in developing countries. 2002. Participants in the 2001 conference on ethical aspects of research in developing countries. *Science 298*: 2133–234

Faunce, T.A., and H. Nasu. 2009. Normative foundations of technology transfer and transnational benefit principles in the UNESCO Universal Declaration on Bioethics and Human Rights. *The Journal of Medicine and Philosophy* 34: 296–321.

FDA. Center for Drug Evaluation and Research. 2001. Guidance for industry: Acceptance of foreign clinical studies. Mar 2001. http://www.fda.gov/RegulatoryInformation/Guidances/ucm124932.htm. Accessed 1 Nov 2012.

Federman, D.D., K.E. Hanna, and L.L. Rodriguez (eds.). 2002. *Responsible research: A systems approach to protecting research participants*. Washington, DC: The National Academies Press.

Fischer, B.A. 2006. A summary of important documents in the field of research ethics. *Schizophrenia Bulletin* 32(1): 69–80.

Garrafa, V., and C. Lorenzo. 2008. Moral imperialism and multi-centric clinical trials in peripheral countries. *Cadernos de Saúde Pública* 24(10): 2219–2226.

Glantz, L.H., G.J. Annas, M.A. Grodin, et al. 1998. Research in developing countries: Taking "benefit" seriously. *The Hastings Center Report* 28(6): 38–42.

Goodyear, M.D.E., K. Krleza-Jeric, and T. Lemmens. 2007. The Declaration of Helsinki: Mosaic tablet, dynamic document, or dinosaur? *British Medical Journal* 335: 624–625.

Gunson, D. 2009. Solidarity and the universal declaration on bioethics and human rights. *The Journal of Medicine and Philosophy* 34: 241–260.

Häyry, M., and T. Takala. 2005. Human dignity, bioethics and human rights. *Developing World Bioethics* 5(3): 225–233.

Hutton, J.L. 2000. Ethics of medical research in developing countries: The role of international codes of conduct. *Statistical Methods in Medical Research* 9: 185–206.

Hyder, A.A., S.A. Wali, A.N. Khan, et al. 2004. Ethical perspective of health research: A perspective from developing country researchers. *Journal of Medical Ethics* 30: 68–72.

ICH-GCP. 1996. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use, ICH Harmonised Tripartite Guideline – Guideline for Clinical Practice (ICH-GCP Guideline). Geneva: ICH. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R3_Organisation/M4_R3__organisation.pdf. Accessed 1 Nov 2012.

Katz, J., A.M. Capron, and E.S. Glass (eds.). 1972. *Experimentation with human beings*. New York: Russell Sage Foundation. Cited in Katz, J., A.M. Capron, and E.S. Glass. 2003. The Jewish chronic disease hospital care. In *Ethical and regulatory aspects of clinical research*, ed. Emanuel, E.J., R.A. Crouch, J.D. Arras, J.D. Moreno, and C. Grade, 11–15. Baltimore: Johns Hopkins University Press.

Killen, J., C. Grady, G.K. Folkers, et al. 2002. Ethics of clinical research in the developing world. *Nature* 2: 210–215.

Kimmelman, J., C. Weijer, and E.M. Meslin. 2009. Helsinki discords: FDA, ethics, and international drug trials. *The Lancet* 373(3): 13–14.

Klimovsky, E., P. Saidon, L. Nudelman, et al. 2002. Declaración de Helsinki: sus vicisitudes en los últimos cinco años (The Declaration of Helsinki: Its hitches during the last five years). *Medicina (Buenos Aires)* 62: 365–370.

Kopelman, L.M. 2005. The incompatibility of the United Nations' goals and conventionalist ethical relativism. *Developing World Bioethics* 5(3): 234–243.

Koski, G., and S.L. Nightingale. 2001. Research involving human subjects in developing countries. *New England Journal of Medicine* 345(2): 136–138.

Krleza-Jeric, K., and T. Lemmens. 2009. 7th revision of the Declaration of Helsinki: Good news for the transparency of clinical trials. *Croatian Medical Journal* 50: 105–110.

Landman, W., and U. Schüklenk. 2005. UNESCO declares universals on bioethics and human rights – Many unexpected universal truths unearthed by UN body. *Developing World Bioethics* 5(3): iii–vi.

Leaning, J. 1996. War crimes and medical science. *British Medical Journal* 313: 1413–1415.

Lescano, A.R., D.L. Blazes, S.M. Montano, et al. 2008. Supporting the creation of new institutional review boards in developing countries: The US naval medical research center detachment experience. *Military Medicine* 173: 975–977.

Levine, R.J. 1998. The 'best proven therapeutic method' standard in clinical trials in technologically developing countries. *IRB: A Review of Human Subjects Research* 20(1): 5–9.

Levine, R.J. 1999. The need to revise the Declaration of Helsinki. *New England Journal of Medicine* 341: 531–534.

Lie, R.K., E. Emanuel, C. Grady, and D. Wendler. 2004. The standard of care debate: The Declaration of Helsinki versus the international consensus opinion. *Journal of Medical Ethics* 30: 190–193.

Loff, B., and J. Black. 2000. The Declaration of Helsinki and research in vulnerable populations. *Medical Journal of Australia* 172: 292–295.

London, A.J. 2000. The ambiguity and the exigency: Clarifying standard of care arguments in international research. *The Journal of Medicine and Philosophy* 25(4): 379–397.

Love, R.R., and N.C. Fost. 1997. Ethical and regulatory challenges in a randomized control trial of adjuvant treatment for breast cancer in Vietnam. *Journal of Investigative Medicine* 45: 423–431.

Lurie, P., and S.M. Wolfe. 1997. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. *New England Journal of Medicine* 337: 853–856.

Macklin, R. 2001. After Helsinki: Unresolved issues in international research. *Kennedy Institute of Ethics Journal* 11(1): 17–36.

Macklin, R. 2005. Yet another guideline? The UNESCO draft declaration. *Developing World Bioethics* 5(3): 244–250.

Macpherson, C.C. 2007. Global bioethics: Did the universal declaration on bioethics and human rights miss the boat? *Journal of Medical Ethics* 33: 588–590.

Macrae, D.J. 2007. The council for international organizations and medical sciences (CIOMS) guidelines on ethics and clinical trials. *Proceedings of the American Thoracic Society* 4: 176–179.

Maureen, B., and J. Murray. 2009. Conducting clinical trials in the US and abroad: Navigating the rising tide of regulation and risk. *Squire Sanders*. http://www.squiresanders.com/files/Publication/93acfe25-bc6d-4de3-9fef-d5f81041b6ce/Presentation/PublicationAttachment/64b5a314-4faf-4ad6-a28f-d6f5a610a0e0/SSD_CENTRAL-%2368696-v2-DRAFT_-_White_Paper_-_Conducting_Clinical_Trials_in_the_US_and_Abroad__M__Bennett_.pdf. Accessed 20 Oct 2012.

McIntosh, S., E. Sierra, A. Dozier, et al. 2008. Ethical review issues in collaborative research between the US and low-middle income country partners: A case example. *Bioethics* 22: 414–422.

Mercosur. Resolución Mercosur de Estudios Clínicos.129/96. http://www.bioscience.org/atlases/jourabbr/b.htm. Accessed 26 Sept 2012.

National Bioethics Advisory Committee. 2001. *Ethical and policy issues in international research: Clinical trials in developing countries*. Bethesda: NBAC.

Nicholson, R.H. 2000. If it ain't broke don't fix it. *The Hastings Center Report* 3: 1.

Normile, D. 2008. Clinical trials guidelines at odds with US policy. *Science* 322: 516.

Nuffield Council of Bioethics. 2002. *The ethics of research related to healthcare in developing countries*. London: Nuffield Council of Bioethics.

Nuffield Council of Bioethics. 2005. *The ethics of research related to healthcare in developing countries. A follow-up discussion paper*. London: Nuffield Council of Bioethics.

O'Neil, P. 2008. Ethics guidelines for clinical trials to be revised. *Canadian Medical Association Journal* 178(2): 138.

Page, A. 2000. Prior agreements in international clinical trials: Ensuring the provision of drugs and other research benefits to developing countries. Background paper prepared for the National Bioethics Advisory Commission. Cited in Macklin 2001.

Participants in the 2001 conference on ethical aspects of research in developing countries. 2002. Fair benefits for research in developing countries. *Science* 298: 2133–2134.

Ramsay, S. 2000. World Medical Association strengthens Declaration of Helsinki. *Lancet* 356: 1389.

Rawlison, M.C., and A. Dochin. 2005. The quest for universality: Reflections on the Universal Draft Declaration on Bioethics and Human Rights. *Developing World Bioethics* 5: 258–266.

Red, P.A.R.F. 2005. *Good clinical practices: Document of the Americas*. Washington, DC: PAHO.

Redbioética-UNESCO. 2008. *Carta de Córdoba sobre ética en investigaciones con seres humanos*. Córdoba: Redbioética UNESCO. 18 Oct.

Rid, A., and H. Schmidt. 2010. The 2008 Declaration of Helsinki – First among equals in research ethics? *The Journal of Law, Medicine & Ethics* 38(1): 143–148.

Rothman, K.J., K.B. Michels, and M. Baum. 2000. For and against. Declaration of Helsinki should be strengthened. *British Medical Journal* 321: 442–445.

Selgelid, M.J. 2005. Universal norms and conflicting values. *Developing World Bioethics* 5(3): 267–273.

Shapiro, H.T., and E.M. Meslin. 2001. Ethical issues in the design and conduct of clinical trials in developing countries. *New England Journal of Medicine* 345(2): 139–142.

Sidle, J.E., E. Were, K. Wools-Kaloustian, et al. 2006. A needs assessment to build international research ethics capacity. *Journal of Empirical Research on Human Research Ethics* 1(2): 23–38.

Skene, L. 2007. Undertaking research in other countries: National ethico-legal barometers and international ethical consensus statements. *PLoS Medicine* 4(2): e10.

Snead, O.C. 2009. Bioethics and self-governance: The lessons of the Universal Declaration on Bioethics and Human Rights. *The Journal of Medicine and Philosophy* 34: 204–222.

Stockhausen, K. 2000. The Declaration of Helsinki: Revising ethical research guidelines for the 21st century. *Medical Journal of Australia* 172: 252–253.

Tealdi, J.C. 2006. Historia y significado de las normas éticas internacionales sobre investigaciones biomédicas (History and meaning of international ethics norms regarding biomédica research). In *Ética de la Investigación en Seres Humanos y Políticas de Salud Pública (Research ethics in humans and public health policies)*, ed. G. Keyeux, V. Penchaszadeh, and A. Saada, 33–36. Bogota: Universidad Nacional de Colombia-Unibiblos-UNESCO.

Temple, R. 2003. Impact of the Declaration of Helsinki on medical research from a regulatory perspective. Address to the Scientific Session, World Medical Association General Assembly. Sept 2003.

Temple, R., and S.S. Ellenberg. 2000. Placebo-controlled trials and active-control trials in the evaluation of new treatments, Part 1: Ethical and scientific issues. *Annals of Internal Medicine* 133: 455–463.

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. *The Belmont report: Ethical principles and guidelines for the protection of human subjects of research*. Washington, DC: Department of Health, Education and Welfare.

Toebes, B. 1999. Towards an improved understanding of the international human right to health. *Human Rights Quarterly* 21: 661–679.

Trotter, G. 2009. The UNESCO Declaration on Bioethics and Human Rights: A canon for the ages? *The Journal of Medicine and Philosophy* 34: 195–203.

Ugalde, A., and N. Homedes. 2009. Discrepancies around Helsinki: Are we missing the point? *Clinical Trial Magnifier* 2(3): 106–111.

UNAIDS, Joint United Nations Program on HIV/AIDS. 2000. *Ethical considerations in HIV preventive vaccine research. UNAIDS guidance document*. Geneva: UNAIDS.

United Nations. 1948. Universal declaration of human rights. GA Res 217 A (III). UN doc A/810 1948 71.

United Nations. 1966a. International covenant on civil and political rights. GA Res 2200ª (XXI). UN GAOR suplemento (no 16) 52. UN doc A/6316. UNTS 999:17.

United Nations. 1966b. International covenant on economic, cultural and social rights. UNTS 993:3. GA Res 2200ª (XXI) UN doc A/6316.

Vollmann, J., and R. Winau. 1996. Informed consent in human experimentation before the Nuremberg cod. *British Medical Journal* 313: 1445–1447.

Wendler, D., E.J. Emanuel, and R.K. Lie. 2004. The standard of care debate: Can research in developing countries be both ethical and responsive to those countries health needs? *American Journal of Public Health* 94(6): 923–928.

Williams, J.R. 2005. UNESCO's proposed declaration on bioethics and human rights – A bland compromise. *Developing World Bioethics* 5(3): 210–221.

WMA. Declaration of Helsinki. http://www.wma.net/en/60about/70history/01declarationHelsinki/index.html. Accessed 2012

Wolinsky, H. 2006. The battle of Helsinki. *European Molecular Biology Organization* 7(7): 670–672.

World Medical Association (WMA). International code of medical ethics. http://www.wma.net/en/30publications/10policies/c8/index.html. Accessed 21 Sept 2012.

Zion, D., L. Gillam, and B. Loff. 2000. The Declaration of Helsinki, CIOMS and the ethics of research on vulnerable populations. *Nature Medicine* 6(6): 615–617.

Zumla, A., and A. Costello. 2002. Ethics of healthcare research in developing countries. *Journal of the Royal Society of Medicine* 95(6): 275–279.

Chapter 3
Globalization and Clinical Research in Latin America

Nuria Homedes and Antonio Ugalde

The globalization of pharmaceutical clinical trials lags behind that of other industries because, until relatively recently, low- and middle-income countries did not have the safeguards the industry needed. Traditionally, clinical trials took place in high-income countries (United States, Europe, Japan and Australia) and the pharmaceutical industry, before gathering clinical trial data in other countries, had to ensure that the regulatory agencies of the countries where 80 % of the pharmaceuticals are consumed (United States, Europe and Japan) would accept the trial results from low- and middle-income countries (Eastern Europe, Latin America, Asia) included in the applications for market authorization.

Another requirement was the existence of adequate systems to ensure the integrity of the research and the protection of intellectual property. The approval of the guidelines from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH GCP) in 1996 (ICH 1996) and the adoption of the Agreement on Trade-Related Aspects of Intellectual Property Rights (WTO 1994) (Virk 2009; Glickman et al. 2009) satisfied the needs of research sponsors. Clinical trials now take place anywhere in the world, and it is expected that the number of trials conducted in low- and middle-income countries will increase significantly in the near future.

This chapter will describe the need for globalized recruitment, the development of clinical trials in Latin America and the factors contributing to the expansion of clinical trials in the region, and finally the consequences that this process may have for the countries and for the participants will be discussed.

N. Homedes (✉)
School of Public Health, Division of Management Policy and Community Health, University of Texas Houston Health Science Center, El Paso, TX, USA
e-mail: nhomedes@utep.edu

A. Ugalde
Department of Sociology, University of Texas, Austin, TX, USA

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_3,

3.1 The Need and Extend of Globalized Recruitment

The pharmaceutical companies like other businesses move some of their operations to other countries to reduce costs, but more importantly, the pharmaceutical industry needs to recruit trial participants in low- and middle-income countries because it is unable to enroll sufficient participants in high-income countries. The need for trial participants has escalated as a result of the increase in the number and sample size of the research protocols. Between 1981 and 1984, the pivotal trials included in the applications for market authorization included an average of 1,321 participants, while in 1994–1995 the average sample size was 4,237 (Department of Health and Human Services 2000). Karlberg (2008a) estimated that it was necessary to enroll about 1,282,000 clinical trial participants yearly, and, since many trials last more than one year, the total number of participants at any given moment is much greater. In 1999, there were 2.8 million people enrolled in industry-sponsored clinical trials, by 2005 there were 19.8 million (Value of Insight 2009), and between 2006 and 2008 this number increased by another 40 %.

Other reasons to recruit in low- and middle-income countries include the industry's need to: (1) comply with the requirements of the U.S. Food and Drug Administration (FDA); (2) accelerate recruitment to reduce the duration of the clinical trials and the cost of research and development (R&D), and (3) open the market for the new products in the countries where they are tested.

To limit the effects of confounders, the FDA recommends limiting the participation of patients on treatment and those having participated in other trials, in favor of people not exposed to medications. It is difficult to find subjects with these characteristics in high-income countries with universal access to health services and medications, but they are found more readily among the uninsured in the United States and in low- and middle-income countries, where a large proportion of the population is not able to obtain the medications they need.

The clinical trial recruitment centers are concentrated in high-income countries, where they compete to enroll the same subjects. For example, in the United States there are 120 centers per million population, in Canada, 92, and in Holland, 85. Argentina is the emerging nation with the greatest density of recruitment centers at 19 centers per million population, but in many other countries there are less than 10 per million (6.2 in Mexico; 4 in Brazil; 0.7 in India, and 0.4 in China)[1] (Thiers et al. 2008). The fact that few residents in low- and middle-income countries have participated in trials and they do not have adequate access to medications results in a considerable pool of eligible participants.

Increases in the sample size of the clinical trials and restrictions in the inclusion criteria lengthen the duration of the trial, increasing the cost of R&D and reducing the period of market exclusivity for the new product granted by the patents.[2] While

[1] The low number of recruitment centers might be partially explained by the fact that in some middle- and low-income countries, clinical trials are also conducted in large public facilities.

[2] Patents are granted before the beginning of the clinical phase, and in most countries are valid for 20 years.

in 1970, it took about 11.6 years of R&D to bring to the market a new molecule; in 2001, 14.9 years were necessary. This means that the period of market exclusivity of a new product was reduced by 3.3 years. At the same time, the cost of R&D has soared, in some estimates by 8 % annually (David et al. 2010) but others give figures up to 14 % (Department of Health and Human Services 2000), and the clinical trials account for between 60 and 70 % of this cost (Value of Insight 2009).

The increasing R&D costs, coupled with the measures implemented by several governments to control the cost of pharmaceuticals, can negatively affect industry's profits. Pharmaceutical companies are looking for ways to counteract this tendency. It has been calculated that for every day of delay in the commercialization of a medication, the industry loses US$1.3 million in income (Rowland 2004). One strategy with big potential impact is to shorten the period of clinical investigation. To that effect the industry uses a variety of methods, such as using electronic information systems to facilitate data transmission between the research centers and the administrative offices of the clinical trial; standardizing templates of contracts with researchers – or with intermediaries – to reduce as much as possible the period of negotiation[3] (National Cancer Institute 2008), and developing systems to hasten recruitment of clinical trial participants (Bloch et al. 2006; Downing 2009).

Hastening recruitment is an important strategy because delays at this stage are a major component of lengthening the duration of the trials. Almost 78 % of clinical trials fail to meet the deadlines for participant recruitment (Department of Health and Human Services 2000). In the United States, only 7 % of clinical trials begin as scheduled; 70 % are delayed for more than one month, and 70 % fail to recruit all the participants required (Value of Insight 2009). Information differs, but it is probable that fewer than 50 % of studies reach their recruitment goal, or meet their objectives without extending the recruitment phase. McDonald et al. (2006) reviewed 114 clinical trials, and found that only 31 % reached their goal and 53 % were extended.

The most important strategies to improve recruitment include: increasing the participation of private sector researchers; utilizing firms specialized in clinical trials management – Contract Research Organizations (CROs); providing incentives for rapid recruitment, and increasing the pool of eligible participants by facilitating the inclusion of residents in low- and middle-income countries (Department of Health and Human Services 2000).

In 1995, 80 % of clinical trials financed by the pharmaceutical industry took place in academic centers, but by the year 2000 this had fallen to 50 %. The private sector, including the CROs, recruit more rapidly than public or private academic centers, in part because the ethical approval of the protocol is faster (Department of Health and Human Services 2000), in many cases taking less than one week and occasionally only a couple of days. The pharmaceutical industry considers that the most important task for the CRO, more so than complying with study protocols, is to complete the

[3] A well-accepted contract template is that used in the United Kingdom for contracts between the public hospitals and the pharmaceutical industry go to www.dh.gov.uk/en/Researchanddevelopment/A-Z/DH_4002073#_1

recruitment of patients by the given date (Cutting Edge Information 2009). Recruitment in low- and middle-income countries can reduce the duration of a clinical trial by six months (Bailey et al. 2006) or even more, as is illustrated in the following estimate by Value of Insight. In the United States, only between 3 and 5 % of cancer patients take part in trials, and if all patients were to be recruited in the USA, in the most optimistic scenario and without taking into account that some eligible patients are already participating in a trial, it would take 5.8 years to recruit sufficient participants to complete a Phase III study, but if patients in low- and middle-income countries are included, the trial might be completed in 1.9 years (Value of Insight 2009).

As an incentive to rapid recruitment, the standard contracts between sponsors, intermediaries, and researchers have been modified. Currently, payments depend on the number of recruited participants, amounts payable to cover fixed costs have been reduced and the commissions increased, and instead of assigning a certain number of recruits per center, competition among recruitment centers is encouraged. Moreover, the number of participants recruited can determine the order of authors in publications (Department of Health and Human Services 2000). It is known that in Latin America there are researchers who recruit their own patients, even to the point of reviewing medical records in public facilities to identify possible participants; some pay other physicians per patient referred, and some contact academic centers to recruit students when healthy participants are needed. Other methods include the use of media to advertise and broadcast information about the study, frequently exaggerating the possible benefits without including the risks, and offering money to participants (Department of Health and Human Services 2000). Another method is to recruit all eligible participants saying that they could refuse to participate (opt-out system), and later put pressure to retain them by means of home visits or telephone calls (Treweek et al. 2010). The incentives for the investigators are also a concern because they might lead to including patients who do not fulfill the inclusion criteria or to retaining patients who should be excluded due to adverse events (McDonald et al. 2006), with the consequent underreporting of safety information.

In addition to accelerating the recruitment process, when clinical trials are conducted in low- and middle-income countries the cost of R&D is automatically reduced because the per patient cost is 40–60 % (Glickman et al. 2009; Bloch et al. 2006) and according to some sources even 90 % less expensive than in traditional countries (Hanauer 2009). However the savings are not as pronounced in Latin America, where the cost per person enrolled is between 70 and 80 % of the cost in high-income countries (Bruce 2008). The most important advantage offered by low- and middle-income countries is the possibility of recruiting and retaining participants, thereby accelerating the commercialization of new products.

It is also hoped that recruiting participants in other countries will facilitate market penetration of new pharmaceutical products. Regulatory agencies might be more willing to grant marketing authorizations if the clinical trials have taken place in their country, and studies show that physicians tend to write prescriptions for products which they have used in their own research (Glickman et al. 2009; Medical News Today 2005).

The pharmaceutical industry projects that by 2020, 50 % of the market growth will take place in low- and middle-income nations; and between 15 and 18 % will come from Latin America (RAPS Webcasts 2009), specifically from Mexico,

Brazil, and Argentina, which consume 80 % of the regional market for medications (Bruce 2008).

Governments, researchers, and patients in low- and middle-income countries welcome the clinical trials. Governments want industry investments (Marshall 2008; Normile 2008), researchers have the opportunity to augment their income and, in some cases, increase their professional prestige or advance academically, and for many patients participation in a clinical trial is their only means to receive the treatment they need. But the circumstances surrounding the implementation of clinical trials in these countries could contribute to the violation of ethical principles governing human experimentation and could lead to the exploitation of the most vulnerable groups.

3.2 Clinical Research in Latin America

The population of Latin America is 589 million (2011), 70 % reside in large metropolitan areas, and 30 % are under 15 years of age. Eighty percent of the population and 90 % of clinical trials in the region are concentrated in six countries – Argentina, Brazil, Chile, Colombia, Mexico, and Peru (Hurley et al. 2009). The inhabitants of four cities alone account for 40 million people (Mexico DF, Rio de Janeiro, Sao Paulo, and Buenos Aires). The population concentration, together with major medical centers and well qualified researchers, is very attractive to the pharmaceutical industry because it facilitates the recruitment of many participants in a few research centers, simplifies logistics, and reduces cost per participant. In addition, the FDA has an interest in studies of Hispanics because it is projected that by 2020 they will be 25 % of the USA population. Japanese regulatory agencies are interested in the data from Peruvian clinical trials, because of the number of Japanese emigrants to that country.

3.2.1 The Evolution of Clinical Trials in Latin America

The implementation of clinical trials in Latin America, with the exception perhaps of Costa Rica (see Chap. 8) occurred quietly for several decades. Laws and regulations for clinical trials are recent, often still incomplete and many are undergoing revisions and amendments. Brazil (Nishioka 2006) and Argentina are countries with more developed regulations (Virk 2009). This author notes that regulations in Mexico are also well advanced, but, as is illustrated in Chap. 10, progress is very slow.

There is no precise regional information on the number of on-going clinical trials, the molecules involved, the number and socio-economic characteristics of the participants, or of the qualification of the researchers. There are four Latin American registries (Argentina, Brazil, Cuba and Peru), and only those of Brazil and Cuba comply with the minimum criteria of the World Health Organization (WHO) and are primary registries.

As of July 1, 2005, the USA government requires that the protocols of all clinical trials, except Phase 1 and most of Phase 4, implemented in the USA and of products that will request market authorization in the USA be registered at the federal registry that is maintained by the National Library of Medicine (www.clinicaltrials.gov). The number of registered trials increased dramatically after September, 2005, when the editors of the leading medical journals announced that a requirement for publication of the results of trials and other themes related to the implementation of trials was that the protocol had been previously registered in the federal registry. Since October 2005, and despite excluding those implemented outside the USA that will not be used to request market authorization in the USA, the USA registry is the most comprehensive registry in the world.

In addition to the themes mentioned above, the FDA registry has other limitations. It includes different types of clinical trials[4] and it is not easy to find only those related to medications. In some cases the site of the proposed study is not included and does not provide the number of participants to be recruited by country. Due to these issues different researchers searching for the same type of information may obtain different results (David et al. 2010; Karlberg 2008b). In spite of this limitation we will use the FDA registry in this chapter because is the most comprehensive for Latin America.

Table 3.1 illustrates the growth of clinical trials of medications registered on the USA registry. Pharmaceutical trials increased overall by 47 % between 2006 and 2008. We can see the greatest increase occurred in high-income countries. The percentage of all clinical trials that are being conducted in Latin America has decreased from 9 % of the total in 2005 to 5 % in the first five months of 2010.

3.2.2 Infrastructure Development for the Implementation of Clinical Trials in Latin America

The infrastructure for clinical trials has grown more rapidly in Latin America than in other parts of the world. In this region, approximately 1,500 recruitment centers are opened each year (Bruce 2008), and Karlberg (2008b) states that between 2006 and 2007 Colombia had the greatest growth in the number of centers in the world (200 %), Brazil was in eighth place (100.3 %) followed by Mexico (96.7 %), Chile (94 %), Argentina (89.7 %) and Peru (82.9 %). However, in 2007 almost half of the recruitment centers (36,281, or 48.7 %) were in the United States, and only 17 % in low- and middle-income nations. In Latin America there is an average of two recruitment centers per million inhabitants (RAPS Webcast 2009). In April 2007, the Latin American countries with the highest number of recruitment centers were Argentina (757, or 1 % of the worldwide total), Brazil (754), Mexico (683), Chile (179), Peru (125), and Colombia (119) (Thiers et al. 2008). The recruitment centers

[4] Clinical trials for diagnostic tests, medical devices and surgical procedures are also included.

Table 3.1 Pharmaceutical clinical trials, by place and study phase, 2006–2010

	2006			2007			2008			2009			2010 (May 31)		
	No.	%[a]	% Phase I and II	No.	%[a]	% Phase I and II	No.	%[a]	% Phase I and II	No.	%[a]	% Phase I and II	No.	%[a]	% Phase I and II
Total	8,064		43	9,558		45	11,856		43	11,260		47	4,523		42
Canada	804	10	37	716	7	43	962	8	38	830	7	43	263	6	45
USA	4,243	53	50	4,845	51	53	6,090	51	50	5,316	47	52	1,880	42	49
Europe	2,242	28	36	2,628	27	40	3,107	26	40	3,111	28	45	1,210	27	39
Japan	196	2	37	220	2	45	284	2	46	287	3	45	111	2	46
Latin America	690	9	27	661	7	28	883	7	25	764	7	25	222	5	31
Rest of world[b]	2,098	26	28	2,276	24	32	2,748	23	29	2,658	24	32	1,005	22	30

Source: Table prepared from the database of Clinicaltrials.gov, selecting pharmaceutical trials only

[a]Totals exceed 100 % due to multicenter trials taking place in various regions or countries

[b]All other countries combined (excluding Latin America, Canada, Europe, Japan and the USA)

Table 3.2 Researchers in FDA-regulated studies by geographic area and growth since 1996

	Number of researchers en 2006	% del total	Annual growth between 1996 and 2006 (%)	Annual growth between 2004 and 2007 (%)
North America	14,555	63.2	1.8	−5.2
Western Europe	3,923	17.0	7.5	−6.1
Central and Eastern Europe	1,793	7.8	41.4	15.9
Latin America	1,095	4.8	27.3	12.1
Asia and Pacific	1,054	4.6	25.6	10.2
The rest of the world	617	2.7	11.0	3.9
Total	23,037	100.1		

Source: Hurley et al. (2009)

in Brazil conducted about five clinical trials per year, followed by Argentina (4.6), Mexico (3.8), Colombia (2.6), Peru (2.5), and Chile (2.2) (Karlberg 2008b).

The growth of the market for clinical trials in Latin America is reflected also in the increase in the number of Contract Research Organizations (CROs) located in the region, in the number of Latin American researchers listed in clinical trials registered with the USA registry, and in the number of researchers who participate in clinical trials regulated by the FDA.

CROs are multinational organizations specialized in managing clinical trials and tend to share the economic risk of not completing a clinical trial as scheduled with the study sponsor. This has been a high growth industry, partly because they have managed to reduce the duration of the clinical trials by four or five months which might represent between US$120 and US$150 million additional income for the pharmaceutical industry. In 2010, CROs administered one third of the R & D budget of clinical trials (Association of Clinical Research Organizations nd).

The number of foreign researchers, that is, those residing outside the USA, listed in research protocols approved by the FDA increased between 1990 and 1999 from 270 to 4,458 (1,600 %) (Department of Health and Human Services 2000). In 2006, Latin America had 1,095 researchers in FDA-regulated studies (4.8 % of the total) (see Table 3.2). The United States and Europe are still home to between 70 and 80 % of researchers conducting FDA-regulated research (Value of Insight 2009; RAPS Webcast 2009).

3.2.3 Growth of the Number of Latin American Participants in Clinical Trials

Data show that the number of participants in clinical trials taking place in low- and middle-income nations has increased in the last several years. One estimate is that 40 % of clinical trial participants live in these countries (Hurley et al. 2009) and, in 2007, 10 % of clinical trial participants were Latin Americans (Bruce 2008). These estimates are based on special studies. The public registries – including the USA registry- do not include information on the number of participants expected to be recruited in each country or region, and the regulatory agencies in Latin American countries do not provide access to this type of information.

While the percentage of all worldwide trials that are conducted in Latin America appears to have decreased, the number of participants has increased. The apparent contradiction can be explained as follows. According to the FDA registry most clinical trials with less subjects (phases 1 and 2) take place in the high-income countries, where they represent more than 40 % of all trials; in Latin America three of every four trials are phases 3 and 4, which involve a significantly higher number of subjects.[5] According to Karlberg (2009a), while each recruitment center in the United States enrolls an average of seven participants per clinical trial, in Latin America the average enrollment is 11 or 12 participants per clinical trial per study site.

The Inspector General of the Department of Health and Human Services of the USA recently published the results of a study of the applications for market authorization of new medications reviewed by the FDA during 2008. The study showed that foreign participation, especially from Latin America, had increased considerably (Department of Health and Human Services 2010). According to this study, the FDA received 129 applications of market authorization. Eight applications did not specify the countries in which the trials had taken place and were excluded from the analysis. Eighty percent of the requests included data collected outside the USA (8 % had data collected only outside the USA, and 72 % included data from both the USA and other countries), and 20 % only contained data from within the USA. Fifty-four percent of participating study sites and 78 % of the clinical trial participants were outside the USA. Of the foreign participation, 60 % of the study sites and 58 % of study participants were from Western Europe, and 7 % of the sites and 26 % of participants were from Latin America. Foreign participation was greater for biological than chemical products, perhaps because clinical trials for vaccines tend to have larger samples.

3.2.4 Financing of Clinical Trials in Latin America

We were not able to find information about the growth and distribution of spending on clinical trials around the world. Kline (2001) reports that in the year 2000, Latin America received only 1.6 % of industry's budget for R&D. A more recent study estimates that only 3 % of R&D money is spent in low- and middle-income countries; or 4.1 % if pre-clinical studies (usually conducted in industrialized countries) are excluded (Value of Insight 2009). This is a very small proportion of the amount allocated by the pharmaceutical industry to R&D of new medications.[6]

[5] Phase I studies typically involve between 20 and 100 healthy volunteers; Phase II between 100 and 500 patients, and Phase III between 1,000 and 5,000 patients. The average cost per person enrolled in Phase I, II, and III trials is US$5,000, US$6,500, and US$7,600 respectively. The size and cost of Phase IV trials varies greatly, typically including thousands of participants. A considerable proportion of Phase IV trials has the marketing of the new product as its principal objective (Charlish and Fritsch 2009).

[6] Financial data presented by the industry on R&D expenditures have been questioned because it is not known what is included in this category. It is possible that there is frequent inclusion of items where marketing the product is the principal objective, including some Phase IV clinical trials.

Table 3.3 Number of clinical trials by region or country and source of financing (in percentages): 2006 – May 31, 2010

Region/country	Year	Number of trials	Industry	University/ organization	USA Federal Government
Canada	2006	804	67	32	12
	2007	716	70	35	8
	2008	962	73	32	5
	2009	830	67	38	6
	2010	263	57	50	2
USA	2006	4,243	52	47	30
	2007	4,845	53	54	24
	2008	6,090	56	48	20
	2009	5,316	54	52	19
	2010	1,880	52	55	17
Europe	2006	2,242	59	47	2
	2007	2,628	58	48	1
	2008	3,107	59	47	6
	2009	3,111	55	49	1
	2010	1,210	49	55	0
Latin America	2006	690	84	13	7
	2007	661	83	17	5
	2008	883	82	19	2
	2009	764	73	26	4
	2010	222	63	33	6
Japan	2006	196	74	23	3
	2007	220	81	19	0
	2008	284	80	19	0
	2009	287	82	19	0
	2010	111	86	13	0
Rest of World	2006	2,098	74	44	6
	2007	2,276	68	27	3
	2008	2,748	67	28	3
	2009	2,658	58	37	2
	2010	1,005	54	44	3
Total	2006	8,064	52	50	18
	2007	9,558	52	53	14
	2008	11,856	55	49	11
	2009	11,260	51	53	11
	2010	4,523	49	54	9

Source: Table prepared from the database of Clinicaltrials.gov, selecting pharmaceutical trials only. Studies may be financed directly by the industry, by universities or organizations, by the Federal Government of the USA, or by a combination of sources. Percentages exceed 100 % due to clinical trials with more than one source of financing

Table 3.3 illustrates the growth of clinical trials and their funding sources per region. On a general level, there is a decrease in the number of trials financed by the USA Federal Government, a small decline in those financed directly by the pharmaceutical industry, and an increase of less than 10 % in studies funded by

universities and organizations (including foundations, patient organizations, and groups seeking solutions for specific diseases). The source of funding for the clinical trials sponsored by universities and organizations is not known, and it is possible that some is provided by the pharmaceutical industry. Analysis by region shows that industry funding has fallen most in Latin America and the countries forming the "rest of the world", while funding from universities and organizations shows the highest increase in Europe, Canada, and Latin America. The industry continues to finance most studies conducted in Japan.

In summary, the available information is incomplete, but seems to indicate that although there is much talk about exporting clinical trials to low- and middle-income countries including Latin America, at present most of the research continues to be done in high-income countries (see Box 3.1). However, we see a steady increase in the number of Latin Americans participating in clinical trials, and given the investments in infrastructure to promote clinical trials in the Latin American region, the need for the industry to have its products on the market as quickly as possible, and the interest of governments and researchers in capturing part of this market, it can be expected that the number of clinical trials taking place in Latin America will increase and even more the corresponding number of trial participants. The information obtained from trials in this region will become more and more influential in the decisions made by the regulatory agencies in high-income countries.

Box 3.1: Clinical Research: Sponsors and Locations

- 50 % of studies presented to the FDA to request the marketing authorization of a product include data collected outside the USA
- 76 % of Phase I clinical trials take place in the USA, Canada, and Holland
- 83 % of research takes place in Europe, North America, and Oceania
- In 2008, 70 % of FDA-approved researchers were residents of the United States or Western Europe
- In 2007, pharmaceutical companies which are members of PhRMA (Pharmaceutical Research and Manufacturers of America) invested only 3 % of funding for research and development in low- and middle-income countries. The percentage increases to 4.1 % if pre-clinical studies are excluded (they are often conducted in industrialized countries and represent 27.3 % of the total cost)
- In 2008, 49 % of expenditures on research and development went to the USA, and 37 % to Western Europe

Source: Value of Insight (VOI 2009).

3.3 Regulation of Clinical Trials in Latin America

The legal and regulatory framework for clinical trials in Latin America is in a process of continuous change in most countries, partly to adjust to the needs of the industry and to better compete against other low- and middle-income countries. In general terms all the countries have developed a regulatory framework consistent with the standards of The International Conference on Harmonization of Good Clinical Practice (ICH-GCP), and promote compliance with the declarations and ethical principles endorsed by governments and medical associations. These include the ethical principles established by the Council for International Organizations of Medical Sciences (CIOMS 2002), the UNESCO Universal Declaration on Bioethics and Human Rights (UNESCO 2005), and the Declaration of Helsinki (World Medical Association nd).

From this common base, each country has established different regulatory mechanisms which are described in greater detail in the different chapters of this book. Here we only want to highlight aspects that favor the implementation of industry-financed clinical trials in various countries of the region, and the circumstances that might lead to the implementation of clinical trials with weak designs and fewer guarantees of protection for study participants in some countries and not in others.

Given that one of the industry objectives is to recruit participants as quickly as possible, we expected the pharmaceutical industry to be interested in conducting clinical trials in countries with the greatest number of eligible participants and bureaucracies most able to expeditiously approve the implementation of the trials. Table 3.4 shows that Brazil and Argentina take most time to authorize participant enrollment, while Mexico, Chile, and Colombia respond most rapidly. In Mexico, the process is fast when the clinical trial is processed only through the Ministry of Health, but more time is needed when Social Security facilities and researchers are involved. From industry data, Colombia is the country which offers least opposition to the use of placebos, while Brazil has led an international campaign against their use (see Chap. 7).

Ethical review of research protocols is a major part of the clinical trial authorization process. Institutional Ethical Committees take between four and eight weeks to review a protocol and question about one third, generally to clarify or modify aspects of the informed consent and only occasionally due to concerns about the study design. In Chile the process can take from six to ten weeks. Ministries of Health and regulatory agencies, and in Brazil the National Ethics Committees (CONEP) may request more information before authorizing the implementation of a clinical trial, but the frequency varies greatly by country. Mexico and Colombia question few protocols (less than 5 %), Peru and Chile request additional information for more than 35 % of the proposed studies, and Argentina and Brazil request clarifications for 75 % of the protocols. Most questions by national authorities tend to be administrative, that is they are related to the presentation of documents, followed by problems of informed consent, especially when the clinical trial involves a vulnerable population, and only Brazil and Argentina question the study design (RAPS Webcasts 2009).

Table 3.4 Weeks required prior to enrolling participants in clinical trials in Latin America, by country

	Mexico	Brazil	Peru	Colombia	Argentina	Chile
Translation to Spanish or Portuguese	2–3	3–5	2	2–3	2–3	2–3
Approval by Ethics Committees	4–6	5–8[a]	5–7[b]	4–5	2 IEC 2 IRB	6–10
Approval from the Ministry of Health	6–8	18–23[c]	10–14	8–10	17–18	4–6
Permission for importation	0		2–3	2	1–2	
Process of importation	1–2 days	2–4	1	1	1–2	2
Total weeks	13–17	31–41	20–27	17–21	25–29	14–21
Comments	More time is needed if IMSS facilities are part of the study	Limited use of placebo. Post-trial treatment is required	Increased inspections. Focus on the credentials and the number of clinical trials per researcher	Placebo accepted if approved by the Ethics Committee	Phase II studies with vulnerable populations or complex designs require 2–4 weeks extra	Vaccine studies require approval from the Immunization Program

Source: RAPS Webcasts (2009)

IEC institutional or Independent Ethics Committee, *IRB* Institutional Review Board

[a]Following Ethics Committee (CEP) approval, another week is needed to prepare the documents for ANVISA

[b]Includes 1 week of delay to send the letter from the ethics committee to the Director of the hospital

[c]This number includes the time required to receive the approval of the Ministry of Health and the importation permit

The relative weight of the approval process in Brazil and Argentina appears to have little influence in the desire of the pharmaceutical industry to conduct clinical trials in these countries. According to an index developed by the consulting firm A. T. Kearney (Bailey et al. 2006), in 2006 Brazil and Argentina were the Latin American countries most attractive to Big-Pharma. The index is based on the following variables and weights:

- The patient pool (30 %)
- The cost-efficiency of the investment (labor, infrastructure and travel communications) (20 %)
- The legal and regulatory framework. This is based on the FDA perspective, the laws and regulations in the country, and systems of protection of intellectual property (20 %)
- Experience in implementing clinical trials: the number of CROs based in the country, number of completed clinical trials, and the availability of professionals (15 %)
- The existing infrastructure, including the quality of the health sector infrastructure, the communication and transportation networks in the country, the intellectual property protection system and other risk factors that could affect the implementation of the clinical trial (15 %)

These data show that the industry prioritizes countries where there is a large pool of participants, it is possible to maximize the use of technology and transportation networks to maintain the flow of information obtained, and to accelerate the other stages of the clinical trial; all without sacrificing the quality of the ethical review and the implementation of the study. This does not stop the industry from pressuring the ethical committees and the regulatory agencies to reduce the time needed to issue authorizations, as for example in Brazil, where the process was modified to allow the approval by the institutional and national ethics committees to proceed simultaneously instead of sequentially, reducing by some weeks the ethical committee approval process (see Chap. 6). The negative aspects of hastening the process include weakening existing protection systems. What has not been clarified is if the pressure to expedite the implementation of clinical trials comes entirely from the pharmaceutical industry, or also from governments who want to maximize foreign investment in their country, or from researchers who receive very large payments and fringe benefits from the implementation of the clinical trials.

3.4 Does Latin America Offer the Necessary Conditions to Protect Those Involved in Clinical Trials?

While the legal and regulatory frameworks established by the Latin American countries may be considered adequate if not yet perfect, there is little information about their functionality and there are no strategies to systematically evaluate the

clinical trial implementation process and correct identified weaknesses. The only information that is periodically collected and can be accessed through the webpage of the FDA refers to the recruitment centers that have been certified by the Office for Human Research Protections (OHRP) in the United States, and the reports from FDA inspections. The results of inspections by national regulatory agencies, the industry, and ethics committees are considered confidential and are not made available to the public.

Of all the recruitment centers throughout the world (74,500), only 9,953 (13 %) are certified by the OHRP, and the majority of these (7,631, or 79 %) are situated in the USA and only 340 in Latin America (Karlberg 2009b). The certificate is granted to the ethics committees that complete an administrative process, including the registration of the Ethics Committee with OHRP and filling up an application; this certificate permits access to financing from United States government agencies. Obtaining the certificate could indicate that the center is able to assess the clinical trials in accordance with internationally accepted ethical principles, but this interpretation would be misleading. A recent study by a U.S. government agency demonstrated that the system is highly vulnerable, as OHRP certification was obtained by a non-existent ethics committee (Government Accountability Office 2009). We do not know the significance it may have, but it is noteworthy that non-USA cities with the largest number of OHRP certified centers are Buenos Aires and Beijing, exceeding many European and Canadian cities which have been conducting clinical research for years (Karlberg 2009b).

The FDA has 200 inspectors to monitor all research centers worldwide, and has recently opened additional field-offices in various countries including three in Latin America: a regional office with three employees in Costa Rica, and offices in Mexico and Chile, each with one employee. The newly recruited staff is responsible for monitoring all the products exported by Latin America to the USA, as well as factories making pharmaceuticals for export, and are not expected to have a significant impact on the supervision of clinical trials.

A report by the Inspector General of the Department of Health (Department of Health and Human Services 2007) notes that one of the problems faced by the FDA is its limited authority to supervise clinical trials implemented outside the USA. Inspections are conducted when the pharmaceutical company requests the authorization to market the product; this is, after the implementation of the trial is completed. The objective of an inspection is to verify that the trial has taken place in accordance with FDA guidelines, and to check the accuracy of the information submitted by the company to the FDA. In 2008, the possibility that a research center in the USA was inspected by the FDA was 16 times greater than that of a foreign center (Department of Health and Human Services 2010).

Against expectations, the results of inspections in Latin America have been better than those in the United States and Europe. Between 1997 and 2008, the FDA completed 3,304 inspections; 81 (2.5 %) in Latin America. As a result of the Latin American inspections, the FDA found serious problems needing immediate response in two centers, and in 44 centers suggested voluntary improvements related to adherence to the research protocols (28), deficiencies in information

systems (25), inadequate information about secondary effects (9), and problems with informed consent (5) (Karlberg 2009c). These inspections are not very effective, partly because they are bureaucratic and as indicated conducted after the trial has been completed. Karlberg (2009c) reported that in 68 % of cases FDA executives downplayed the importance of observed problems. The overall positive information from the FDA about the implementation of trials contrasts with testimony from regional experts, with the few academic publications and media reports about this issue, and with the opinions of the authors of the different chapters included in this book.

One question (not addressed in this book but which should be considered) is whether all the clinical trials in progress around the world are necessary for the advancement of science, or if they expose people to unjustified risk. There appears to be a disproportion between the increase in the number of clinical trials being implemented and the decrease in treatment innovation that has taken place during the last decade. Obviously, studies involving the use of drugs in humans without the objective of advancing the existing therapeutic arsenal could not be considered ethical and they represent a waste of resources. The same reasoning applies to clinical trials with inadequate study designs, among which some authors include the non-inferiority trials (Garattini and Bertele 2007). Not offering the best available treatment to all patients may have a negative impact on participants, and could contribute to promoting expensive medications in place of other more economical treatments with the same or better efficacy and safety profiles.

Several researchers argue that pharmaceutical clinical trials conducted by the industry in Latin America are not aimed at finding solutions to regional disease priorities (Perel et al. 2006). From our perspective this concern loses relevance as the epidemiological transition progresses, since the ailments affecting the population of Latin America increasingly resemble those of residents in industrialized countries. A comparison of the principal causes of death in Latin America, Europe, and the USA shows many similarities. The fact that patients can be quickly recruited in Latin America confirms that clinical trials do seek treatment for diseases affecting the Latin American population. Nevertheless, the need for increased R&D to find treatments for rare and neglected diseases should not be downplayed, and prices for new treatments must not be a barrier for those who need them, especially those who have participated in their discovery.

The following is a summary of the problems that have compromised the ethical implementation of clinical trials in Latin America, which we have classified in the following categories: secrecy, ethics committees, equitable distribution of benefits and risks, informed consent, the utilization of public infrastructure for private gain, and conflicts of interest.

3.4.1 Secrecy and Lack of Clinical Trial Information

The secrecy surrounding the clinical trials and their ethical assessment is a major impediment for the evaluation of the systems that have been established to protect

clinical trial participants in Latin America and to assess the quality of the data obtained during the trials. Only two national clinical trial registries meet the minimum standards established by the WHO; most are not accessible to the public, they are incomplete, do not differentiate between pharmaceutical clinical trials and other types of research involving humans, and in some cases it is difficult to know if they are reporting the number of protocols or the number of research sites. Available registries do not provide information about studies which have been rejected, and therefore cannot be used to prevent the most controversial clinical trials from taking place in countries with the weakest regulations.

As shown in a recent study (Department of Health and Human Services 2010), not even the FDA has access to detailed information on clinical trials with pharmaceuticals. According to this study, the FDA did not have information that should have been included in the application for market authorization for 29 of the 129 new products included in the sample. Eight of these applications could not be found, and the remaining 21 were incomplete, in some cases omitting the location where the study took place, while others lacked the number of participants or various appendices.

3.4.2 Ethics Committees

There have been functional problems with ethics committees in most countries. Some countries have a registry of ethics committees, very few have an accreditation system, and none have a formal performance evaluation. Brazil has disabled ethics committees that did not meet minimum requirements, and the Peruvian regulatory authority has also banned one committee. The regulations often specify that ethics committee members must be independent of the administration of the institutions in which they are based and must include community representation and experts in clinical research and in bioethics. In practice, this does not always happen.

Rivera and Ezcurra (2001) studied 22 Latin American ethics committees and found that 80 % of their members were contracted by the institution where the committee was operating. In most cases (16 of the 22) members had been nominated by the Directors, and only six committees elected their members. Physicians were heavily represented in most committees and there was little community representation. Other researchers have found similar situations. Valdez-Martinez et al. (2004, 2005, 2006, 2008) studied the ethics committees of the Mexican Social Security Institute (IMSS) and found that most lacked experts in clinical research and bioethics, fewer than half kept minutes of the meetings, more than 50 % of the members had roles as Directors in the IMSS institutions, and the refusal rate for research projects was less than one per thousand. Brazil is considered to have the most advanced and best organized system for the ethical review of research protocols involving humans (Novaes et al. 2008) but it still has problems (Freitas 2006). In several countries of the region, if one ethics committee rejects a project the researcher can seek the approval of other committees until approval is obtained.

While there are well-functioning ethics committees, there are many which do not sufficiently protect study participants, either because they lack the technical capacity to do so or because they respond to the interests of the researchers, study sponsors, or the institutions where the clinical trial will take place (Clarin 2002; Fuentes and Revilla 2007). Moreover, various regional experts have affirmed that committee members who ask too many questions and stimulate controversy during the process of protocol review are dismissed from the committees. Private ethics committees unattached to medical facilities – also known as commercial-, consistent with their mission to facilitate research and ensure their survival by capturing future contracts from study sponsors, tend to do a faster and more superficial review than the institutional committees.

3.4.3 Equitable Distribution of Benefits and Risks

The social class of clinical trial participants is not known, but available information suggests that participants are primarily low-income and indigent, a population generally considered to be "vulnerable". The Pan-American Health Organization (2007:321) estimates that between 20 and 25 % of Latin Americans do not have convenient access to medical care, and people dependent on the public network of services have problems obtaining medications, above all cancer chemotherapy and new medications. As many as 80 % of Brazilians, 55 % of Ecuadorians, 45 % of Bolivians, 40 % of both Argentineans and Peruvians, 30 % of Colombians, and 13 % of Chileans may be in this situation.

In Latin America, two thirds of drug expenditures are out of pocket, and according to a WHO survey, in 60 % of the countries in the region fewer than 80 % of the residents have access to essential medicines (Pan American Health Organization 2007:375). The situation may have improved, especially in Mexico and Argentina, but there continues to be a large pool of patients for whom participation in a clinical trial is the only way of obtaining treatment. People in this situation can be considered "vulnerable", in addition to the majority also being in poverty and with low education levels, and therefore special care needs to be taken when they are recruited to participate in clinical trials.

3.4.4 Informed Consent

All ethical codes include the need to obtain informed consent from study participants, but the lingering question is if persons recruited into clinical trials – including residents in high-income countries – truly understand the possible risks and benefits of participation. Critics say that informed consent materials serve to protect the researcher and study sponsor more than providing information to potential participants. Among researchers responding to a survey by the National

Bioethics Commission of the United States, 13 % reported that they did not know if their clinical trial participants from low- and middle-income countries understood that they were part of a research study (Amnesty International 2003). Other studies in the Latin American region (Petinelli 2005; Vargas-Parada et al. 2006) and the case studies described in this book have documented problems in the informed consent process.

Problems of informed consent in Latin America lie deeper than doctor-patient communication by itself. For example, the ability of patients to make truly independent decisions when the study may be their only path to treatment, and when the attending physician recruits his or her own patients for a clinical trial has been questioned. In Latin America, most patients have a good relationship with their physician (Center Watch Newsonline 2006; Rodrigues 2007), often trust their recommendations, and they may sometimes feel threatened and agree to participate in a study from fear of reprisals which could compromise their medical access. Participants in clinical trials also receive benefits that can influence their decision to take part in a study, such as transportation between their home and the clinic, reimbursement of expenses (including food), and the more rapid attention in a possibly more luxurious facility than in the public sector. The perception is that participation in a clinical trial means better treatment and better quality services than those offered in the public sector. Taken together, these circumstances may explain the double retention rates of patients in low- and middle-income countries compared with patients in high-income countries (Kline 2001).

Communication problems between researcher and patient and the lack of truly informed consent to participate in a study can affect the data collected and the clinical trial results. Problems of compliance with treatment have been reported because patients have not been able to read the instructions sufficiently well. Patients may also use traditional medicines, or have a reaction without notifying the researcher, especially when a study participant does not know his or her diagnosis and does not know the information needed by the researcher (Virk 2009).

3.4.5 Using Public Infrastructure for Private Benefit

This book includes several examples of researchers recruiting clinical trial participants in the public sector and using public facilities and personnel for recruitment and during the clinical trial, a problem that has been documented by other authors (Rodrigues 2007). The contracts between the trial sponsor, or their intermediaries, and the investigator state that all costs associated with the study will be borne by the sponsor, but this does not address the possibility that patients, recruited from the public sector, rely on the public sector to take care of the adverse events occurred during their participation in the study, or that for reasons of convenience investigators use public sector resources without informing the study sponsor. There are countries where the study sponsor reimburses public sector expenses and also contributes to improvements in the infrastructure of the facility

where the clinical trials are being implemented (Normile 2008). The problem may not be reluctance on the part of study sponsors to accept financial responsibility, and a solution may lie in involving institutional administrators during contract negotiations with the sponsor or their intermediaries.

As we have seen and will be documented in greater detail throughout the book, conflicts of interests affect how clinical trials are approved and implemented.

3.5 Discussion

Research and development of medications and medical technology requires clinical trials with human subjects and, as long as they are needed, the pharmaceutical industry will continue to be interested in recruiting participants in middle- and low-income countries, including Latin America. A question asked by both ethicists and critics is: What benefits does the Latin American population obtain from participating in clinical trials? One answer is that for many people with few resources, the trials give access to medications which they may not otherwise receive. The counter-argument is that the pharmaceutical industry is taking advantage of the failure or negligence of governments, because the right to health is guaranteed in the Constitution of most Latin American countries.

Often, study participants do not know that they can be assigned to a control group, which would mean that they will not be receiving the "new pharmaceutical," and maybe if they had a better understanding of the methodology they would have decided not to participate. Another question is for how long these participants will benefit from participating in a trial. Without guaranteeing access to the new drug when proved to be effective and safe, and given that most participants are people with few resources, the high prices for patented medicines preclude patients from accessing the treatment they helped develop.

A question for the regulatory agencies is: how good is the data obtained from clinical trials taking place in Latin America? This question cannot be answered with any precision because there are no external systems for supervision once the ethics committees and the regulatory agencies approve a clinical trial. The quality of the data is totally in the hands of the researchers, the CROs and the pharmaceutical industry. Contracts between the industry and the CROs and those with the researchers emphasize rapidity in recruitment and completion of the studies, which encourages enrollment of patients who do not meet inclusion criteria and retention of patients who may have wanted to withdraw or should have been withdrawn from the study. There is a need for Latin America to assure that the countries benefit from studies conducted on its residents and to develop systems for supervision of clinical trials while they are in progress; a task for the regulatory agencies, ethics committees or other independent agencies (that is without conflicts of interest) charged with monitoring the clinical trials could conduct.

With clinical trial regulation having significant gaps or poor implementation in many countries, non-compliance with internationally accepted ethical principles is

facilitated. These lapses are ignored by those who benefit from the clinical trials – the industry, the CROs, and the researchers. The lack of transparency which characterizes the region may be the result of lobbying by those who benefit from clinical trials and from the status quo. In addition to implementing publicly accessible clinical trial registries, ethics committees and study participants must also have access to clinical trial financial information, including the benefits for the principal investigator and the recruiters.

Ethics committee operations are also deficient, especially when final approval – or not – depends on the decisions of commercial ethical committees. The growing complexity of the evaluation process requires the establishment of national or regional processes for scientific and ethical review of clinical trials, and communication mechanisms are needed between the regulatory agencies of different countries in the region to ensure that questionable studies do not move towards the countries with the weakest regulations.

There are reasons to question the participation in clinical trials of a disproportionate number of poor for the benefit of residents and corporations of high-income countries and wealthy Latin Americans. Three alternatives are suggested to curtail this unethical pattern: (1) a moratorium on the recruitment of low-income Latin Americans, who are the most frequent clinical trial participants, and the development of strategies to recruit participants among those who are most likely to benefit from clinical trial results, or a balanced participation of all income groups; (2) establish systems to ensure that clinical trial participants understand the consent forms and are aware of the risks of participating in an experiment and that they may not benefit from participation in the study, and (3) work passionately to ensure that the pharmaceutical industry is committed to register new medications in the countries where the studies took place and to sell them at affordable prices for everyone.

It is important for the industry to establish systems assuring good administration of clinical trials and respect for the dignity of study participants. If this is neglected, the regulatory agencies in countries where most sales take place (United States, Europe, Japan and Australia) could reject the data from low- and middle-income countries.

References

Amnesty International. 2003. A bitter pill. *Amnesty International Magazine*, Summer.

Association of Clinical Research Organizations (ACRO). nd. CRO Market. www.acrohealth.org/cro-market1.html. Accessed 28 Oct 2012.

Bailey, W., C. Cruickshank, and N. Sharma. 2006. Make your move: Taking clinical trials to the best location. *A.T. Kerney Executive Agenda*, 56–62. http://www.atkearney.com/main.taf?p=5,1,1,116,3,1/. Accessed 30 June 2009.

Bloch, M., A. Dhankhar, and S. Narayanan. 2006. Pharma leaps offshore. *McKinsey and Company*. http://www.mckinseyquarterly.com/Pharma_leaps_offshore_1787. Accessed 28 Oct 2012.

Bruce, F. 2008. Latin America: Ripe for clinical research? *Scrip 100*, December 8, 92–93. http://content.yudu.com/Ay6ty/Scrip-100-Dec08/resources/92.htm. Accessed 28 Oct 2012.

Center Watch Newsonline. 2006. Fighting the Logjam in LatAm Drug Trials, September 18. http://www.centerwatch.com/news-online/article/573/fighting-the-logjam-in-latam-drug-trials. Accessed 28 Oct 2012.

Charlish, P., and S. Fritsch. 2009. All they're cracked up to be? Scrip 100, Sript's analysis of the pharmaceutical industry's performance and prospects. London: Informa UK, December, 115–117.

CIOMS. 2002. International ethical guidelines for biomedical research involving human subjects. http://www.cioms.ch/publications/layout_guide2002.pdf. Accessed 28 Oct 2012.

Clarín. 2002. Un informe sobre ética en las investigaciones con pacientes oncológicos de la defensoría del pueblo de la nación de Argentina denuncia que el estado no controla pruebas de drogas en pacientes con cáncer (A report by the Argentina's national ombudsman regarding the ethics of research on cancer patients denouncing that the government does not control clinical trials), May 22. http://www.saludyfarmacos.org/lang/es/boletin-farmacos/boletines/jun2003/etica-y-medicamentos/. Accessed 28 Oct 2012.

Cutting Edge Information. 2009. Strategic Clinical outsourcing. Selecting partners and managing relationships. http://www.cuttingedgeinfo.com/research/clinical-development/outsourcing-selection-strategy/. Accessed 26 Oct 2012.

David, E., T. Tramontin, and R. Zemmel. 2010. The road to positive R&D returns. *McKinsey Quarterly*. http://www.mckinseyquarterly.com/The_road_to_positive_R_and_D_returns_2528. Accessed 28 Oct 2012.

Department of Health and Human Services. Office of Inspector General. 2007. The Food and Drug Administration's oversight of clinical trials. OEI-01-06-00160. https://oig.hhs.gov/oei/reports/oei-01-06-00160.pdf. Accessed 28 Oct 2012.

Department of Health and Human Services. Office of Inspector General. 2010. Challenges to FDA's ability to monitor and inspect foreign clinical trials. OEI-01-08-00510. http://www.healthlawyers.org/News/Health%20Lawyers%20Weekly/Documents/06_25_10/oei-01-08-00510.pdf. Accessed 28 Oct 2012.

Department of Health and Human Services. Office of Inspector General. Recruiting Human Subjects. 2000. Pressures in industry-sponsored clinical research. OEI-01-97-00195. http://firstclinical.com/regdocs/doc/?db=OTH_OEI_01_97_00195. Accessed 28 Oct 2012.

Downing, G. 2009. Designation of clinical research information integration as an objective of "meaningful use" of electronic health record systems. Presentation to the HIT Policy Committee, Office of the Secretary. Department of Health and Human Services, 28 Oct. http://healthit.hhs.gov/portal/server.pt/gateway/PTARGS_0_10741_907422_0_0_18/Downing-UMPClincalResearch.pdf. Accessed 28 Oct 2012.

Freitas, C.B.D. 2006. O sistema de avaliação da ética em pesquisa no Brasil:estudo dos conhecimentos e prácticas de lideranças de Comités de Ética em Pesquisa (System of research ethics evaluation in Brazil: Study of knowledge and practices of leadership of research ethics committees). Dissertation, Universidad de Sao Paolo.

Fuentes, D., and D Revilla. 2007. Acreditación de comités de ética en investigación, como parte de un proceso (The process of accreditation of research ethics committees). *Anales de la Facultad de Medicina (Peru)* 68(1): 67–74. http://sisbib.unmsm.edu.pe/bvrevistas/anales/v68n1/pdf/a09v68n1.pdf

Garattini, S., and V. Bertele. 2007. Non-inferiority trials are unethical because they disregard patients' interests. *Lancet* 370: 1875–1877.

Glickman, S.W., J.G. McHutchison, E.D. Peterson, et al. 2009. Ethical and scientific implications of the globalization of clinical research. *New England Journal of Medicine* 360: 816–823.

Government Accountability Office (GAO). 2009. Human subjects research: Undercover tests show the institutional review board system is vulnerable to unethical manipulation. GAO-09-448T. http://www.gao.gov/products/GAO-09-448T. Accessed 27 Oct 2012.

Hanauer, S.B. 2009. Outsourcing clinical trials. *Nature Reviews Gastroenterology and Hepatology* 6: 191.

Hurley, D., M. Lipezker, H. Melgar, et al. 2009. Latin American clinical trial authorizations. Overview and update. *Regulatory Focus* 38–42.

ICH. 1996. Guidance for the industry. E6 good clinical practice: Consolidated guidance. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf. Accessed 22 Sept 2012.

Karlberg, J.P.E. 2008a. Industry clinical testing of new medicinal products requires 95.000 study sites and 1,300.000 subjects annually. *Clinical Trial Magnifier* 1(6): 101–109.

Karlberg, J.P.E. 2008b. Globalization of sponsored clinical trials. *Nature Reviews Drug Discovery* 7: 458. doi:10.1038/nrd2441-c1.

Karlberg, J.P.E. 2009a. What is driving the globalization process of clinical research? *Clinical Trials Magnifier* 2(8): 396–397.

Karlberg, J.P.E. 2009b. Office of human research protection assurance. *Clinical Trials Magnifier* 2 (8): 418–433.

Karlberg, J.P.E. 2009c. USFDA site inspections findings, 1997–2008, fail to justify globalization concerns. *Clinical Trial Magnifier* 2(4): 194–212.

Kline, D. 2001. Clinical trials in Latin America. *DataEdge*. http://www.fast-track.com/pdfs/ClinicalTrialsLatinAmerica.pdf. Accessed 27 Oct 2012.

Marshall, E. 2008. Lemons, oranges, and complexity. *Science* 322: 209.

McDonald, A.M., R.C. Knight, M.K. Campbell, et al. 2006. What influences recruitment to randomised controlled trials: A review of trials funded by two UK funding agencies. *Trials* 7(1): 9.

Medical News Today. 2005. US Drug companies conducting more clinical trials overseas to reduce costs, speed approval. *Medical News Today*, 18 May. www.medicalnewstoday.com/articles/24634.php. Accessed 27 Oct 2012.

National Cancer Institute. 2008. Initiative to speed clinical trial negotiations moves forward. *NCI Bulletin* 5: 20. http://www.cancer.gov/aboutnci/ncicancerbulletin/archive/2008/100708/page1. Accessed 27 Oct 2012.

Nishioka, S.A. 2006. Regulação de pesquisa clínica no Brasil: passado, presente e futuro (Regulation of clinical research in Brazil: Past, present and future). *Prática Hospitalar* 8(48): 17–26.

Normile, D. 2008. The promise and pitfalls of clinical trials overseas. *Science* 322: 214–216.

Novaes, M.R., D. Guilhem, and F. Lolas. 2008. Dez anos de experiência do comitê de ética em pesquisa da Secretaria de Saúde do Distrito Federal, Brasil. *Acta Bioethica* 14(2): 185–192.

Pan American Health Organization. 2007. *Health in the Americas*. Washington, DC: PAHO.

Perel, P., J.P. Casas, Z. Ortiz, and J.J. Miranda. 2006. Noncommunicable diseases and injuries in Latin America and the Caribbean: Time for action. *PLoS Medicine* 3(9): e34.

Petinelli, A. 2005. Irregularidades en proyecto epidemiológico (Irregularities in epidemiological project). *Boletín Fármacos* 8(4): 107–110.

RAPS Webcasts. 2009. Drug development in Latin America. Recent trends and competitive advantage. http://www.docstoc.com/docs/50709074/Webcast_FocusLatam_1_. Accessed 28 Oct 2012.

Rivera, R., and E. Ezcurra. 2001. Composition and operation of selected research ethics review committees in Latin America. *IRB Ethics and Human Research* 23(5): 9–12.

Rodrigues, D.G. 2007. Clinical research and drug development in Latin America: Weighing the pros and cons, talking about the future. *Journal of Investigative Medicine* 55: 223–229.

Rowland, C. 2004. Clinical trials seen shifting overseas. *International Journal of Health Services* 34(3): 555–556.

Thiers, F.A., A.J. Sinskey, and E.R. Berndt. 2008. Trends in the globalization of clinical trials. *Nature Reviews Drug Discovery* 7: 13–14.

Treweek, S., E. Mitchell, M. Pitkethly, et al. 2010. Strategies to improve recruitment to randomized controlled trials. *Cochrane Database System Review* 4. http://www.thecochranelibrary.com/userfiles/ccoch/file/INternational%20Clinical%20Trials%20Day/MR000013.pdf. Accessed 27 Oct 2012.

UNESCO. 2005. Declaración Universal de Bioética y Derechos Humanos. Paris: UNESCO. http://unesdoc.unesco.org/images/0014/001461/146180s.pdf. Accessed 27 Oct 2012.

Valdez-Martínez, E., J. Garduño-Espinosa, H. Martinez-Salgado, et al. 2004. Local research ethics committees of the Mexican Institute of Social Security: Results of a national survey. *Public Health* 118: 329–336.

Valdez- Martínez, E., B. Turnbull, J. Garduño-Espinosa, et al. 2005. Understanding the structure and practices of research ethics committees through research and audit: A study from Mexico. *Health Policy* 74(1): 56–68.

Valdez-Martínez, E., B. Turnbull, J. Garduño-Espinosa, et al. 2006. Descriptive Ethics: A qualitative study of local research ethics committees in Mexico. *Developing World Bioethics* 6(2): 95–105.

Valdez-Martínez, E., A. Lifshitz-Guinzberg, and J. Medesigo-Micete. 2008. Los comités de ética clínica en México: la ambigua frontera entre la ética asistencial y la ética en investigación clínica (The clinical ethics committees in Mexico: Unclear frontier between ethical assistance and clinical research ethics). *Revista Panamericana de Salud Pública* 24(2): 85–90.

Value of Insight (VOI). 2009. The case for globalization: Ethical and business considerations in clinical research. https://www.voiconsulting.com/sites/default/files/publication-popups/Clinical%20Trials%20Globalization%20-%20ACRO.pdf. Accessed 27 Oct 2012.

Vargas-Parada, L., S. Kawa, A. Salazar, et al. 2006. Informed consent in clinical research at a general hospital in Mexico: Opinions of the investigators. *Developing World Bioethics* 6(1): 41–51.

Virk, K.P. 2009. Latin America's trials climate. *Applied Clinical Trials online*. http://license.icopyright.net/user/viewFreeUse.act?fuid=ODg1NDQwNg%3D%3D. Accessed 27 Oct 2012.

World Medical Association. nd. Declaration of Helsinki. http://www.wma.net/en/30publications/10policies/b3/

WTO. 1994. Agreement on trade-related aspects of intellectual property rights. Annex 1C. http://www.wto.org/english/docs_e/legal_e/27-trips.pdf. Accessed 22 Sept 2012.

Chapter 4
The Regulatory Framework and Case Studies from Argentina

Antonio Ugalde and Nuria Homedes

Argentina is a federation of 23 provinces and the autonomous City of Buenos Aires, which is the Capital of the country. Argentina has an estimated population of 41.029 million (2010), largely of European descent and has one of Latin America's lowest growth rates (1.05 %). Eighty percent of the population resides in cities or towns of more than 2,000, and over one-third lives in greater Buenos Aires. In 2009, the official poverty level was 13.2 %. Argentina's constitution mandates a separation of powers into executive, legislative, and judicial branches at the national and provincial level.

Each province and the federal capital of Buenos Aires have representative governments and their own constitutions that abide by the claims, rights and guarantees of the national Constitution. Each Province and the federal capital are responsible for its health sector, retaining all power and authority in health matters that are not expressly delegated to the national government.

The rate of highly qualified physicians per population is one of the highest in the world (3.16 per 1,000 inhabitants in 2004). The quality of hospitals is uneven. Some in wealthy metropolitan areas have the latest technology and very well trained physicians, while many of the hospitals in poor provinces do not meet the standards as centers for research involving humans. Argentinean physicians perceive their salary as being too low and are eager to participate in clinical trials to complement their income. Similarly, since many citizens experience difficulties accessing needed medications, there is a large pool of potential study participants.

The authors appreciate the valuable comments from Sergio Eduardo Gonorazky, Gonzalo Moyano, Liliana Virginia Siede, Juan Carlos Tealdi, and Susana Vidal. The authors have sole responsibility for the analysis and interpretation of data.

A. Ugalde
Department of Sociology, University of Texas, Austin, TX, USA

N. Homedes (✉)
School of Public Health, Division of Management Policy and Community Health, University of Texas Houston Health Science Center, El Paso, TX, USA
e-mail: nhomedes@utep.edu

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_4,

4.1 Number and Characteristics of Clinical Trials in Argentina

Table 4.1 shows the number of clinical trials which, according to the National Administration of Food, Drugs and Medical Technology (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica or ANMAT), were authorized in Argentina between 1994 and 2006. The table presents the information by study phase, study design, and sponsor, but the registry does not allow distinguishing the clinical trials with medications from other studies involving humans.

The information differs from that on clinicaltrials.gov, which is based on studies with medications presented to the Food and Drug Administration (FDA) and is shown in Table 4.2. The USA registry lists fewer trials than ANMAT's, partly because the FDA does not include all the studies that are not conducted in the USA or all Phase IV trials, it did not include Phase I studies until 2008, and because Table 4.2 was prepared excluding all non-pharmacological trials. Both databases show that the number of Phase I trials conducted in Argentina is limited.

Table 4.1 Clinical trial characteristics: percent, 1994–2006

Study phase	Phase 1	Phase 2	Phase 3	Phase 4	Biological	Total number
	3 %	17 %	55 %	20 %	5 %	1.894
Study design	Open	Double blind	Blind			
	2 %	59 %	39 %			1.894
Sponsored by:	International pharmaceutical	National pharmaceutical	Independent researchers	CRO/SMO		
	69 %	13 %	7 %	18 %		1.571

Source: Pérez (2008)

Table 4.2 Characteristics of clinical trial protocols, Argentina, 2005–2010

	2005	2006	2007	2008	2009	Totals[a]
Number of registered clinical trials	31	53	54	52	24	214
Phase I			1	1		2
Phase II		5	10	11	6	32
Phase III	29	44	40	36	17	176
Phase IV	2	4	3	3	1	13
Sponsored by:						
Pharmaceutical industry	31	49	52	51	25	208
National Institutes of Health and other federal agencies, USA		1		1		
Other organizations and Universities		6	4	4	1	15
With placebo (in the title)			1	3		4
Studies in children <18 years	5		8	5	5	23

Source: www.clinicaltrials.gov Table prepared by authors
[a]Some protocols may include various phases of a clinical trial

Table 4.3 Number of clinical trial participants, 2007–2009

	Number of patients
2007	34,901
2008	22,640
2009	30,464

Source: Quiñones (2010)

According to the FDA registry, the number of clinical trials being conducted in Argentina was stagnant between 2006 and 2008, and fell to less than half in 2009. Information obtained from the Argentine Chamber of Medicinal Specialties (CAEMe) shows that, despite the drastic reduction in the number of clinical trials approved in 2009, the number of study participants in 2009 was higher than in 2008 (see Table 4.3).

Until the National Ministry of Health Resolution 102 was passed in 2009 creating the Registry for Clinical Trials with Human Subjects, the public did not have access to information about the clinical trials taking place in Argentina. There is documentation suggesting that prior to that date the estimates were inaccurate. For instance, Young (2007) documented that ANMAT had not been informed about two of every three trials that were being conducted, and at that time the regulations did not require the registration of Phase IV trials. The oncological trials that will be presented later also indicate that many clinical trials were not registered during the decade of the 1990s.

4.2 A Brief Review of Clinical Trials Regulations: 1997–2010

The first reference to clinical trials in Argentine legislation dates from 1964, when the Law of Medications (No. 16.463/64) was approved. This law states that medications must show their efficacy and safety through controlled clinical trials. ANMAT was established in 1992, during the Presidency of Carlos Menem (1989–1999), as an agency of the Ministry of Health (Law 1490–1992). In the area of medications and medical devices, ANMAT is responsible for the processes of authorization, registration, standardization, supervision, and control of products used in medicine, and for the register of clinical trial protocols. ANMAT houses the National Drug Institute, which, in addition to being responsible for ensuring adherence to good manufacturing practices in the production of medications, also evaluates preclinical information.

According to Article 2 of Law 1490/92, ANMAT has jurisdiction throughout the nation and has to follow the technical and scientific standards set by the Department for Policy, Regulation, and Health Relations of the National Ministry of Health. Clinical trial responsibility lies with ANMAT's Directorate of Medicines and Related Materials (DEMA), which authorizes clinical trials and makes inspections.

In recent years, several provinces have developed their own regulations for clinical trials. The City of Buenos Aires and the provinces of Buenos Aires, Cordoba, Neuquen, and Santa Fe have sanctioned laws; others, such as Mendoza and Salta have ministerial resolutions. In these cases, clinical trials may need approval from the national government and the province.

Presently, there is no national law governing clinical research involving humans, but there are Ministerial Resolutions issued by the Ministry of Health and since the creation of ANMAT many regulations have been introduced, (see Annex 4.1). There is also a Law from the National Ministry of Justice for the protection of personal data, which has a bearing on clinical trials.

4.2.1 Regulation 5330 (ANMAT 1997)

This regulation, approved one year after the approval of the Guide for Good Clinical Practice (ICH E6) by the International Conference on Harmonization (see Chap. 2), establishes that:

- In clinical pharmacological research, the physical and psychological welfare of the clinical trial participants must prevail over the interest of science and of the community, and the research must be conducted in accordance with known scientific principles
- ANMAT authorization is required to conduct
  - Phase I, II, and III clinical pharmacological studies
  - Phase IV studies aimed at determining a new indication, new dosage, pharmacovigilance bioavailability, bioequivalence, and/or other pharmacokinetic studies
  - Phase IV studies with placebo control, and/or conducted in special populations such as neonates, infants, adolescents, and the elderly
- All studies, whether or not ANMAT approval is required, must be approved by an Ethics Committee and by the Committee of Teaching and Research[1] of the institution where the study will take place, and ANMAT must be informed through a sworn statement when a study begins
- The research ethics committees (RECs) must have a minimum of five members, one member representing the community interests, who must not have any association with the center where the clinical trial will take place, and another

[1] Ethics committees may have different names according to institutions. An institution could have an Ethics Committee and a Research and Teaching Committee while other institutions could have a Research Ethics Committee. For example, in one hospital the Research Ethics Committee is known as The Institutional Council for the Review of Research Studies. There are institutions that only have the Committee of Teaching and Research and contract out with an Ethics Committee, most commonly with a private Committee.

who should not be involved in clinical work. The RECs are asked to monitor clinical trials during their implementation to ensure that there are no changes to the protocol and to protect the human rights of trial participants.
- ANMAT has the responsibility not only for approving research, but also for conducting inspections of the study sites, and reviewing the periodic and final reports sent by principal investigators to the study sponsors
- The design of the trial and the principal investigator have to comply with the guidelines established in the Regulation; and follow the procedures for requesting authorization for the trial and for reporting adverse effects. Failure to adhere to the regulations will result in sanctions
- The informed consent form must be signed by the patient in the presence of at least one witness. In the case that a healthy patient or volunteer cannot personally give consent, it must be obtained from someone who meets the qualifications set out in Civil Law to be their legal representative. For children, this would be their parents, and for incapacitated psychiatric patients, it would be their legal representative or, in the absence of a legal representative, a judge
- The patient has to be informed about the objectives, methods, expected benefits, alternative treatments, and possible risks inherent to participating in the study; any problems which may arise; the confidentiality of the information; and that they may withdraw from the study at any time without having to provide any explanation and without any prejudice against them
- The sponsor and/or the researcher promise to provide the medication in the study free of cost

If these conditions are not met, the clinical trial can be canceled immediately in the non-compliant center(s) (see Capitulo V of the regulation).

Among other items, the application for authorization to conduct a clinical trial must include a sworn declaration that the researchers expressly commit themselves to comply with the letter and the spirit of the Code of Nuremberg and the Declarations of Helsinki and Tokyo.

4.2.2 Law 25.326 and Regulatory Decree No. 1558 (National Ministry of Justice 2000 and 2001)

This Law establishes that the National Office for the Protection of Personal Data of the Ministry of Justice has to monitor the informed consent forms to ensure that paragraphs referring to the confidentiality of information meet legal and regulatory statutes. Among other items, the Regulation states that information given to participants must be written in language appropriate for the social and cultural circumstances of the participant. Past and present legislation establishes that infraction of the standards is a sufficient motive for immediate cancellation of the clinical trial, but this has rarely happened.

4.2.3 Regulation 690 (ANMAT 2005)

This Regulation formalized the procedures for conducting clinical trial inspections by ANMAT, for writing the inspection results, and for adjudicating sanctions. It also defines terms, including the description of "vulnerable populations".

The Inspection Guide specifies that the inspector must:

- Review 100 % of consent forms (in all versions) to verify that they were dated prior to the patient's enrollment in the study and were signed by the patients (or their legal representative) and an independent witness
- Check that the study had been approved by ANMAT and by the Committees of Ethics and of Teaching and Research
- Check that consent has been obtained by a member of the research team authorized by the principal investigator
- Confirm compliance with the approved protocol
- Verify the quality and accuracy of the information entered into the clinical history and in the Case Report Form

4.2.4 Resolution 1490 Good Clinical Practice Guide for Research Involving Human Subjects (Ministry of Public Health 2007)

The Resolution places in the Argentinean context the international ethical and scientific standards for the design, implementation, registration and reporting of experimental studies involving humans. This Guide was based on the document prepared by the Pan American Network for Harmonization of Drug Regulations, approved by the Pan American Health Organization (PAHO) on March 4, 2005, which needed to be integrated into ANMAT regulations in order to become mandatory. ANMAT completed this process by issuing Regulation 6677 at the end of 2010.

Resolution 1490 expanded the regulations guiding the constitution and operations of ethics committees, the characteristics of the informed consent and guidance on how to obtain it, the responsibilities of sponsors and principal investigators, and the procedure for the notification of adverse effects. It required the RECs to review the contracts between the study sponsors and the researchers; as well as the contracts with insurance companies, which should cover any potential harm to participants attributable to their involvement in clinical trials.

4.2.5 Regulation 6550 (ANMAT 2008)

The request for ANMAT's approval of a proposed study must include:

- Information about the members of the Ethics Committees involved in the trial (both at the time of its authorization and during its development)

- The plan of the Committees of Ethics and Teaching and Research for monitoring the clinical trials they have approved, which might include observing the process of obtaining the informed consent, and their commitment to forward their evaluations to ANMAT
- Proof that the highest provincial health authority with jurisdiction over the institution that will implement the trial knows that ANMAT is processing the clinical trial authorization and that the highest authority in the institution that implements the trial has authorized it
- Copies of the contract between the sponsor and/or the health center and/or the principal investigator

According to the Regulation, consent forms have to include the following text immediately above the space for the signatures:

> When you sign this form, you are agreeing to participate in an experimental medical research project for clinical pharmacology or medical technology, authorized by the National Administration of Medicines, Food, and Medical Technology (ANMAT). If before signing you have any questions about the explanations given to you by your physician or the Ethics Committee please call "*ANMAT answers*", using its free telephone number 08003331234 or 011 4340 0800 from Monday to Friday, 8:00am - 5:00pm

4.2.6 Regulation 1067 (ANMAT 2008)

This regulation established a new procedure for reporting serious and unexpected adverse drug reactions. It is intended to speed up the transmission of information about the possible adverse effects of the experimental medication arising during the study, in Argentina or worldwide, to ANMAT, the Research Ethics Committees, and the Committees for Teaching and Research.

4.2.7 Resolution 102 (Ministry of Health 2009)

This Resolution established the Registry of Clinical Trials Involving Humans. One objective is to increase transparency in research, to avoid "the production of biases and distortions in the generation and transmission of results…" The Register should be available to the general public. Art. 1 of the Resolution specifies the 22 fields that the Registry should include to offer ample information about the trials to health care personnel in all biomedical areas as well as in science in general.

4.2.8 Regulation 6677 (ANMAT 2010)

This regulation rescinded Regulations 5330/97, 1067/08, and 6550/08, and is the current reference document for the conduct of clinical trials in Argentina. The regulation requires study sponsors and researchers to conduct clinical research

in accordance with the international standards established in the Guide for Good Clinical Practice. In a departure from previous regulations, Regulation 6677 makes reference to the Declaration of Helsinki and ignores Nuremberg and Tokyo. Following the example of the USA Food and Drug Administration (FDA) does not require authorization for Phase IV trials.

The Regulation does no longer require that RECs know and analyze the budget of the proposed trial. However, it requires that payments made to participants for transport, per diem, or other reasons be made available to the REC. The Regulation has removed the need to obtain protocol approval from the Teaching and Research Committee of the institution where the clinical trial will take place; only the approval from the institutional or external REC is now needed. It also excludes – except for vulnerable individuals – the need for a witness to confirm that the recruited person fully understands what participating in a clinical trial entails, including the risks and responsibilities, and that their participation is voluntary.

The glossary of Regulation 6677 defines vulnerable population only as people who could be influenced to participate in a study by the anticipation of benefits or by threats or coercion from a researcher or other dominant person. It does not explain educational, cultural, social, or economical vulnerability, which suggests that social scientists had little participation in the process of writing the Regulation.

Section C, No. 14 states that audits are different from the follow-up procedure required by the RECs:

> The sponsor must implement an auditing process as part of the system of guarantees for the study, with the objective of ensuring that all study activities, including the registration, analysis, and report of the data, are completed exactly in accordance with the protocol, its standard operating procedures and policy and regulatory requirements

The new Regulation states that the consent document must be written in a way that is "clear, precise, complete, truthful, and written in practical and understandable language" (No. 5.2.3), but it does not say who should confirm that these requirements are met.

The requirement to include information for participants on how to contact ANMAT if participants have questions before signing the consent form that was required by Regulation 6550 (2008) was reduced to:

> This clinical pharmacological study has been authorized by ANMAT. If you have any questions about the treatment under investigation, please call *ANMAT answers* at 0800 333 1234 (free telephone call)

During the Mercosur[2] Congress for Bioethics and Human Rights (December 2010), this Regulation was discussed and criticized at length. Leading Argentinean bioethicists considered that it was a regressive step in the history of clinical trial regulation.

[2] Mercosur, the "Common Market of the South", is a trading bloc with four full members – Argentina, Paraguay, Brazil, and Uruguay. Venezuela has not achieved full membership yet. Associate members are Bolivia, Ecuador, Colombia, Chile and Peru. It is the world's fourth largest trading bloc. The population of the full member countries is more than 270 million people, with a collective GDP of US$2.4 trillion (http://www.cfr.org/trade/mercosur-south-americas-fractious-trade-bloc/p12762).

4.3 Implementation of the Legislation

4.3.1 Authorization to Implement Clinical Trials

In 2007, as a result of irregular practices found in clinical trials conducted at the Neuropsychiatric Hospital (to be presented later), the Audit Department of the Autonomous City of Buenos Aires investigated seven hospitals and while reviewing 184 clinical trial protocols found that only 18 % of clinical trials had all the documentation required by ANMAT regulations; in most of the hospitals, clinical trials did not have hospital approval nor had they been authorized by ANMAT, and only 26 % of the clinical trials had insurance policies to cover potential harms to participants, as required by law (Clarín 2007).

The reality contrasts with the statements made to the press by the Director of ANMAT in 2007: "We are the best in the world in the development and control of clinical research protocols. So much so that for the last five years we have coordinated the working group of the Pan-American Health Organization on this topic" (Savoia 2007), adding that from 2000 to December, 2007, ANMAT had initiated 28 investigations and imposed 18 fines (four against the principal investigator and the pharmaceutical company, five against a pharmaceutical company, and nine against a researcher). Most were for missing reports, falsification of information, and irregularities in obtaining informed consent from the patient. The Executive Director thought that the fines were severe. In eight years (2000–2007), the total amount of the fines imposed to industries and physicians was 575,000 and 182,000 Argentine pesos respectively, or an approximate annual average of US$20,500 and US$6,500 (Savoia 2007). Given the amount of money paid to clinical trial researchers and the pharmaceutical industry profits, these cannot be considered punitive fines.

4.3.2 Clinical Trial Inspections

Table 4.4 shows the number of protocols evaluated and approved by ANMAT between 1997 and 2006 (n = 1,113), and the number of inspections carried out during the same period (n = 374). The decision to inspect the trials responds to these criteria (Pérez 2008): clinical trials with participants from vulnerable populations; trials with greatest risk for participants; trials requiring many participants; the history and reputation of the principal investigator; trials conducted in multiple sites, and if there are any reports suggesting safety problems or complaints.

Unfortunately, apart from some anecdotal information to be presented later, inspection findings are not available and therefore it is impossible to assess how much or how little inspections contribute to improving the technical and scientific quality of the clinical trials, to preventing technical or ethical errors, and to protecting the participants – or if the inspections are merely a pro forma administrative act. Argentina's civil society does not know if the number of inspections is correct or not.

Table 4.4 ANMAT inspections of clinical trials, 1997–2006

	Number of protocols evaluated and approved	Number of inspections
1997	116	10
1998	134	17
1999	122	46
2000	161	53
2001	158	54
2002	144	30
2003	119	44
2004	158	44
2005	150	26
2006	223	50
Total	1,113	374

Source: Pérez (2008)

The legislation provides for sanctions when infractions are discovered, but the information about sanctions imposed as a result of routine inspections is not available. Sanctions vary, from warnings to fines, suspension of the clinical trial or closing the trial site, legal action, and/or sanctions from the corresponding professional association.

4.3.3 Research Ethics Committees (RECs)

Before the establishment of ANMAT in 1992, there were few bioethics committees in Argentina; they dealt primarily with medical ethics issues, and were located in the major hospitals of large cities. With the advent of clinical trials, there was an apparent need to form committees to evaluate compliance with ethical standards in research involving humans, and to prepare professionals for the new tasks these committees would perform (Vidal 2004). The adoption of Regulation 5330 in 1997 stimulated the formation of committees and training programs for bioethics in research.

The national government does not register, accredit, or monitor RECs, and there is no National Registry of RECs, nor a National Bioethics Committee. ANMAT can only set the standards the committees have to fulfill before the regulatory agency can accept their recommendations.

Some provinces have a registry of RECs, but only for trials conducted within its own jurisdiction; for example, the Province of Cordoba started its registry in 2002 (see for more details Chap. 5). The Province of Buenos Aires began its registry in 2009, and a system of accreditation was developed later. Accredited RECs that fail to meet performance standards can lose their accreditation. To that effect, the provincial regulatory agency has to monitor the RECs, which is more than a simple administrative process and not always is an easy task. The autonomous federal capital of Buenos Aires has a central Bioethics Committee that can monitor the activities of the RECs but does not evaluate clinical trial protocols.

Several overseas organizations, such as the John E. Fogarty Center for Advanced Study in Health Sciences, at the National Institutes of Health (NIH, USA), have provided bioethics training courses for professionals in Argentina and other Latin American countries (see Chap. 12 for a critical view of these courses). National organizations, some with connections to the pharmaceutical industry, also have provided training courses on good clinical practices. Other agencies, for example, the UNESCO Bioethical Network of Latin America and the Caribbean, give bioethical training courses from the perspective of human rights (Peralta Corneille 2009).

In spite of the bioethics trainings that have taken place, conflicts of interests are found within institutional RECs, as it is very difficult for committee members not to feel pressured by administrators who may benefit from the donation of equipment or other items promised by trial sponsors, or by researchers from their own institution who have a scientific or monetary interest.

In December, 2010, one of the most recognized bioethicists in Argentina said in an interview:

> The Ethics Committees in health institutions still have a confused and uncertain position, and it has happened that hospital directors have dissolved the Ethics Committee because they... rejected an unacceptable research protocol, questioning the independence of RECs (Lipcovich 2010)

4.3.3.1 Private RECs

If the clinical site does not have a REC it can use an external REC and pay for the service. The amount charged varies depending on the number of centers participating in the trial. It has been said that the RECs are responsible for monitoring the implementation of the clinical trials, and therefore they need to be reasonably close to the location where the trials are to be implemented. However, this is not always the case for private RECs.

There are private RECs in institutions that do not provide medical care services. And there are a few RECs that were created to review protocols. Two of these are located in the City of Buenos Aires and together they approve approximately 80 % of all clinical trials. One is the Pharmacological and Medication Research Foundation (FEFyM in Spanish), and the other is the Ethics Committee of Dr. Virgilio G. Foglia, established in 1994 under the auspices of the Center for Studies of the Chemical Pharmaceutical Industry in Argentina (CEDIQUIFA in Spanish) and the Argentine Medical Association.

FEFyM was originally established in the Department of Pharmacology, School of Medicine, University of Buenos Aires. At that time the Director of FEFyM was the Head of the Department and received honoraria directly from the services provided. The Foundation eventually had to leave the University. At present, the FEFyM Ethics Committee has seven members and three associate members, as well as a President and two Vice-Presidents. In 2010, its members included two leading pharmacologists, two psychiatrists (one of whom is also a lawyer), a pediatrician, an internist/rheumatologist, a biologist, a nurse, a lawyer, and a housewife. It is

estimated that FEFyM reviews about 40 % of all clinical trial protocols implemented in the country.

In 2009, FEFyM had an administrative director, two coordinators, and five auditors, while in 2010 the list of auditors on its web site showed only two internal auditors, three external auditors, and three scholarship holders classified as evaluators (medical students in their internship year). FEFyM has published on its web site the number and geographic location (but not the institutions) where audits of clinical trials took place in 2009 (FEFyM 2010). A total of 115 audits were conducted in different provinces of Argentina, and during this process they reviewed the clinical histories (656) and informed consents (1024) of 60 protocols. On its webpage, FEFyM includes a few results of the audits and suggestions to improve clinical trial implementation. However, there is no specific data on the breadth and depth of the audits. The reader does not know if the purpose of the reviews of clinical histories was to check that the records existed, were adequately kept, or that the information had a scientific logic; if the review of informed consents were mainly to verify that they were signed or if they confirmed that consent was actually freely given and truly informed, especially if the trials included vulnerable patients.

The information available suggests that the audits were primarily an administrative activity (mark yes/no/don't know) with comments that could be potentially useful. An example of a comment is: There were an important number of clinical histories that were almost ineligible. We can suggest that the illegibility probably made the review of the records difficult and resulted in problems when trying to verify the validity of the data. From this point of view it is important to know how many of the 656 reviewed clinical histories had this problem and the potential impact on the validity of the data collected during the trial.

The FEFyM website does not include comments and recommendations to ANMAT. In accordance with existing standards, a REC should stop a study if violations of the existing standards are found; for example, if participants had been recruited without their consent, or if consent had been given but it was neither voluntary nor informed; if there had been undue inducements to participation, such as the provision of expensive treatments otherwise not accessible to the patients, and other infringements of the standards. It appears that no trial was stopped as a result of the audits.

Argentinean researchers have questioned the independence of FEFyM and other private external RECs. The Institutional Council for the Review of Research Studies (CIREI), of the Private Community Hospital in Mar del Plata reviewed 36 protocols submitted by the pharmaceutical industry that included the researcher's brochure, the information for the patients, and the informed consent form. Of the 36 protocols, 30 had been previously approved by FEFyM, three by another private non-institutional ethics committee, and three had not yet received approval. At the time, the CIREI was composed of seven physicians, one lawyer, a social worker, a philosopher, and an administrative secretary. Four members had a master's degree in bioethics.

In 85 % of the protocols approved by external private RECs, the CIREI found a total of 92 infractions of ANMAT's standards and regulations. For example, 64 % of the protocols restricted the indemnification for harm attributable to participation in the clinical trial to paying for medical expenses; 42 % of the protocols did not state that the results of the trial would be made public; 24 % did not assume any obligation to participants following the conclusion of the study; 27 % did not include their sources of financing; 12 % considered the possibility of recruiting patients under the age of 21 years, but did not provide consent documents for that age group; and 6 % did not acknowledge the possibility of adverse effects in the informed consent form (Gonorazky 2008). The review concluded by suggesting that the sponsor or researcher selected the REC that would facilitate the approval of the protocol.

Private external RECs know that conforming to the expectations of the study sponsors (the expeditious approval and requiring few changes) increases the possibilities of future contracts. To say it differently, satisfying the client is important to the survival of the private external REC business, and the sponsors quickly learn the RECs that are more favorable to their interests. The potential conflict of interests is there.

4.3.4 Informed Consent

The clinical trials later discussed reveal that participants often signed the informed consent form without always understanding some basic concepts such as placebo or even the experimental nature of a trial. In some cases participants were enrolled in trials before granting their informed consent. Regulations 6650 and 6677 both required the inclusion in the consent form of a statement and a phone number that participants could call to obtain additional information about the trial. The statement begins by describing the study as a clinical pharmacological study. It can be suggested that not all participants understand the meaning of clinical pharmacological study. It might have been better to say: This is an experiment to learn if the medicine will help patients feel better and identify the harms that it can cause. Many protocols list adverse effects but, as will be explained later in the discussion of the COMPAS trial, some participants misunderstood the adverse effects for ills that they will be exposed to if they did not participate in the trial. Communication specialists should 'translate' the lengthy, frequently incomprehensive forms, to meet the level of literacy of those who have to give the informed consent.

The audits of FEFyM explained that:

> Individual (case by case) presentations [of the process of obtaining informed consent] were found only in a very few records, describing in some way the process of invitation, discussion, and asking for informed consent

It would have been necessary to conduct interviews to discover the participants' understanding of the informed consent document, and to find out if they agreed to

participate voluntarily without pressure from treating physicians. It also would have been necessary to find out if the recruiting physicians received any payments, in which case the audit could have been able to identify possible conflicts of interest.

The CIREI in the Private Community Hospital of Mar del Plata uses an interesting strategy to ensure that consent is informed and freely given. Three people not associated with the Hospital, two social workers and a nurse explain the risks, benefits and obligations to patients eligible to participate in the trial. Their function is to ensure that participants completely understand the consent form, and to answer the questions that patients may have before signing the consent form.

4.3.5 Implementation of the Clinical Trial Registry

In compliance with Resolution 102 of 2009, ANMAT began in late of 2010 to publish on its web page the Clinical Trial Registry. The Registry includes information on all clinical trials starting from 2000. Instead of the 22 fields required by the Resolution, it only includes the following: the title of the trial, the sponsor and name of principal investigator, site, therapeutic group, the ethics committee which approved the study, and the year. This limited information is inconsistent with the objectives expressed in Regulation 102 of 2009.

4.4 Questionable Clinical Trials

ANMAT like most regulatory agencies in Latin America does not provide information on the results of the inspections, and most information on ethical problems occurring during the implementation of clinical trials is not accessible. The only information on fines and disciplinary actions that are made public is the results of court cases. In the cases that follow, we summarize information from available summaries and judicial decisions, interviews with past and present ANMAT administrators, statements from administrators and researchers that have been published in a variety of sources, and articles by investigative journalists. Several of these articles gave important information about legislative and ethical violations and caused ANMAT to make field inspections.

4.4.1 Cancer Studies

In 2001, at the Annual Meeting of the American Society of Clinical Oncology (ASCO), Argentine researchers presented several papers on clinical trials conducted in the country. An anonymous complaint to the Argentine Ombudsman indicated that many of the studies had not received authorization from ANMAT (Mondino 2003:67).

According to Argentine laws, the Ombudsman has the responsibility to investigate all accusations presented by citizens, and to prepare a summary of the findings. If legal infractions are found during the investigations, the Ombudsman must present them to the Criminal Court (Mondino 2003:9). In this case, the accusation referred to non-compliance with ANMAT Regulation 3530/97, requiring regulatory agency approval for clinical trials involving humans (Mondino 2003:4).

Following the accusation, the Ombudsman requested information from ANMAT on the status of all the clinical trials discussed at the ASCO meetings between 1998 and 2002, and whose abstracts had been published beforehand in the proceedings of the ASCO Annual Meetings (Mondino 2003:68). The Ombudsman investigated 26 trials presented at ASCO in 2000 and 2001 (the report did not explain the reasons for failing to investigate of the earlier trials as requested by the Ombudsman). Of the 26 trials, nine (35 %) had complied with the regulations (Mondino 2003:11).

The Ombudsman's report, in addition to listing the legal and ethical violations in the investigated trials, questioned the general situation of clinical trials in Argentina and the operative capacity and internal conflicts in ANMAT. It showed conflicting positions between the divisions and departments that had jurisdiction over clinical trials, especially between the clinicians of the Department for the Evaluation of Medications and Related Substances (CEMA in Spanish) and the Bureau of Legal Affairs (DAJ in Spanish).

In the summary of his report, the Ombudsman wrote (Mondino 2003:9):

> . . . beyond the [internal] differences, we can confirm at the same time a handling of internal matters and of the files that were examined, which can best be qualified as indolent, and also an apparent and unconcerned renunciation of the required exercise of control. . . [adding that in the two years 2001-2003, although violations had been identified, no sanctions had been imposed and no measures taken to rectify the situation]. Moreover, members of the Bureau of Legal Affairs (DAJ) told officials of this office [the Ombudsman] that the Ministry of Health and, specifically, the Minister himself, were not aware of the situation in question although regulations require ANMAT to inform the superior authority of events such as those presented here

Following a request for information from the Ombudsman, ANMAT responded that there was no mechanism to determine if clinical trials were conducted in violation of Regulation 5330/97, and that they were unaware of what the technical area of the agency had done about it. The Executive Director of ANMAT affirmed that there was no coordination between the different departments of the regulatory agency (Mondino 2003:69).

The Ombudsman's Report expanded on the apparent disorganization and operative dysfunction of the regulatory agency and wrote (Mondino 2003:70):

> Serious non-compliance and irregularities have been confirmed. . . the Bureau of Legal Affairs, by action or omission, resulted in the lack of application of the rules in ANMAT Regulation 5330/97. Most of the records [prepared by the clinical staff of ANMAT and documenting the violations of the Regulation] suffered unexplained interruption and paralysis in the Bureau of Legal Affairs. . . (with) irrelevant and arbitrary assertions, [the DAJ] tried to restrict as far as possible the powers of the Comptroller of ANMAT, or, what is worse, to change "in practice" the scope of alleviation in the Regulation. . . [and] the higher authorities of the agency did not intervene nor take any measures in respect to the inactivity of the DAJ

The Ombudsman also criticized the incompetence and irresponsibility of the ANMAT administration (Mondino 2003:70):

> Finally. . .we see many administrative irregularities such as inconsistency of dates, missing documents which cannot be traced, overlapping postmarks, and others such as large periods of inactivity and a lack of application of measures which would seem to be pertinent, reasonable, and necessary in accordance with principles stated in the administrative handbook and the care which is expected of a public official. In conclusion, the cases investigated by this Ombudsman. . . show serious omissions on the part of ANMAT consistent with the systematic lack of control over experimentations in clinical pharmacology

Although it has great value, the Ombudsman's Report did not name the principal investigators, the pharmaceutical companies which sponsored the trials, nor the hospitals and clinics where they took place. Most of the medications were patented, and it would have been easy for the Ombudsman or for ANMAT to ask the pharmaceutical companies holding the patents if they sponsored clinical trials of their products in Argentina, and/or request copies of the protocols and information about payments made to the principal investigators. It would have been simple to confirm if the principal investigator had violated Regulation 5330/97.

Several trials used combinations of gemcitabine, cisplatin, paclitaxel, or carboplatin, or combinations of one of these drugs with other medications, to determine if there should be changes in the usual doses or in the combinations of the medications, or to discover new indications. Many of these substances are very toxic, and have serious secondary effects, which may result in a deterioration of the quality of life for the patients. Several of the trials took place with vulnerable patients (the elderly and children).

Three institutions where the trials took place did not respond to ANMAT questionnaires, and the Ombudsman did not require further action. Reasons for not applying for ANMAT's authorization may be grouped into three categories: (1) the studies were not considered to be clinical trials because they used previously approved medications, and the researchers considered that their use in new combinations or for new indications did not constitute a clinical trial. A few studies stated that the use of the medication followed guidelines which had been standardized in many countries, including Argentina; (2) the studies had begun before Regulation 5330/97 became effective; and (3) they were not clinical trials, the medicines were offered as compassionate use of drugs approved for other uses in terminal patients with no other therapeutic alternatives.

In several cases, the researchers said that the study had been approved by the institutional Ethics Committee and/or the Committee of Teaching and Research and that the patient had been informed and given consent, but, except in a few instances the evidence was missing.

There is consensus among researchers, and the Ombudsman agrees, that the prescription of a medication or combination of medications for an unapproved use or at different dosage to 30 or 40 patients, sometimes more than 100, following a methodology that is used in clinical research constitutes a clinical trial. In addition, the medications used in several of the studies were very expensive for public hospitals, and it was unlikely that the hospital administration would have authorized

these costs when their budgets were so limited that at times they could not provide basic medications. During the years when these studies took place (2001–2002) Argentina was suffering one of the worst economic recessions of its history. The scarcity of medicines was such that the chief of pharmacy in a large public hospital in the Buenos Aires metropolitan area explained to the authors (Interview 2003):

> We produce our own medications, under conditions which would not be approved by the Ministry of Health, but the alternative is to leave patients without any

It will be hard to believe that a public hospital would have allocated a part, however small, of its scarce resources for experiments that would not benefit the hospital.

It would be very unusual for the American Society of Clinical Oncology to invite researchers to present the results of cases where approved medicines had been administered for compassionate use or according to the guidelines standardized in the United States, in Europe, and in other countries. The clinicians of the ANMAT Department for the Evaluation of Medications and Related Substances (CEMA) confirmed that there was additional information showing that most of the studies presented by Argentine researchers at ASCO were indeed clinical trials.

Four of the abstracts published in the Proceedings of the American Society of Clinical Oncology, 2001, stated that the papers presented the results of clinical trials. The Director of a center in Salta, which had participated in an international multicenter Phase 2 study, explained to ANMAT that in 1999, there was contradictory information about the efficacy of gemcitabine in bladder cancer and it was important to determine its efficacy and (Mondino 2003:72):

> . . . for statistical reasons, it was important to gather the experience of a good number of patients. . .In good faith, we did not realize that it should have been reported to ANMAT. . .no patient paid for the drug. The company that provided the medication had previously reviewed it. . .as Director of this institution I did not receive any money, not even for the cost of presenting it at the conference

It is very difficult to accept that a clinical researcher did not know that a multicenter international Phase 2 trial should have been approved by ANMAT, in compliance with Regulation 5330/97.

The answer of the Director of the center who coordinated another Phase 2 trial, which took place in various centers in Argentina, and from whom ANMAT had requested information, said (Mondino 2003:102):

> It is a multicenter international study. . .we did not submit it to ANMAT because it was a post-marketing off-label study [a clinical trial of a medication already on the market that was being tested for new indications]

The Teaching and Research Committee of one of the hospitals told ANMAT (Mondino 2003:98):

> It was not considered appropriate to submit information to ANMAT under Article 1, Legislation 150/92, as this study involves a clinical procedure that is not a trial of anything new

Previous data from this same study had been published, however, stating that the data came from a clinical trial. A medical examiner wrote about this study for ANMAT (Mondino 2003:98):

> It is evident that this is a clinical trial, as the authors themselves acknowledge in the title of the project, during the research, and in the publication where they described the results of the same study

Judged by the clinicians of the ANMAT ad hoc Committee, 16 of the 17 studies were clinical trials and the sponsors should have applied for authorization before enrolling patients. For unknown reasons, the Bureau of Legal Affairs did not consider that the regulations had been violated and archived the case.

In his conclusions, the Ombudsman noted the mistakes made by ANMAT in the review process of the 17 clinical oncology trials (Mondino 2003:135–138):

- Not using its power of control to intervene and monitor clinical trials
- Not processing received complaints in a timely manner
- Not informing the Ministry of Health of the situation
- Not applying the law
- Administrative deficiencies added difficulty to unveiling the true facts
- It was not known if patients knew that they were participating in clinical trials
- Not informing the Ministry of Health of possibly criminal violations
- Not checking:
  - If the research was conducted respecting the dignity of the person, if the participants had given consent, and if so, if it was informed consent
  - If any serious secondary effects had occurred during the trials
  - If the clinical trials had included participants from vulnerable populations (neonates, children, adolescents, elderly)
- The sources of funding for the clinical trials, and whether the *Obras Sociales*[3] provided financing, which would have been against the law

One possible explanation is that because ANMAT ignored its own rules and ethical principles, sponsors and researchers interpreted that they also were allowed to ignore its regulations. It is not surprising that four years later, according to its Executive Director,[4] ANMAT still did not know about one third of the clinical trials being conducted in Argentina (Young 2007).

The Argentine Association of Clinical Oncology supports its members unconditionally. Its Board complained to the Director of ANMAT. The Board was upset because ANMAT had investigated the clinical trials that had been conducted without authorization. A letter from the Board said (Mondino 2003:125):

[3] Obras Sociales are organizations that manage the compulsory public health insurance for employees, originally organized through trade unions.

[4] Since 2000, as a result of its administrative dysfunction and internal corruption, ANMAT has had a State-appointed Executive Director, that it is known as *Interventor*.

> . . . many of the presented studies used drugs approved by the appropriate authorities, they were done to investigate if the efficacy and dosage for our patients were the same as those reported in the international literature, tested different methods of administration or dose variations, which can be considered as "off label" use and did not require special approval

The letter attacked the whistle blower saying that his motivations were not scientific but ideological (Mondino 2003:126):

> [His accusation]. . . seems to be the result of the implementation of a campaign whose reasons we do not know and whose purpose we cannot understand. We note that this same professional is on the side of socialized medicine, and regarding the need of approval of conventional national protocols he is a strong supporter of misguided economic policies which seriously affect the best practice of the specialty

The Department for the Evaluation of Medications and Related Substances (CEMA) had shown that all except one of the oncological studies reviewed by its clinical personnel were clinical trials and violated Regulation 5330. That DAJ and other ANMAT authorities ignored their recommendations may have had an impact on the morale of the clinical staff.

4.4.2 The Naval Hospital and the Slow Pace of Justice: The GUARDIAN Trial

Hoechst Marion Russell – which merged with Aventis Pharma and later was acquired by Sanofi – developed the drug cariporide. It was hoped that the medication would protect the heart of patients with coronary angina, and of those who had had angioplasty or bypass surgery. The GUARDIAN clinical trial was approved by the FDA, and took place in 400 centers in 23 countries with a total of 11,500 participants. There were 26 centers in Argentina, one being the Naval Hospital in Buenos Aires; a prestigious hospital with a renowned cardio-vascular department, and about 120 cardiac patients per year.

The principal investigator of GUARDIAN had conducted other clinical trials sponsored by Hoechst Marion Russell and was known for obtaining the rapid approval of the Hospital Ethics Committee. Four other physicians collaborated in this study. The pharmaceutical company expected to recruit 24 patients over 18 months, but the Naval Hospital enrolled 137 patients in half that time. For each patient the principal investigator would receive US$2,700 or a total of US $369,000, a real fortune by the country's economic standards. The amount per patient was similar to what Hoechst was paying per patient enrolled in Canada.

One patient participating in the trial died in each of the following months: December 1997, and January and February 1998. In March, the pharmaceutical company reviewed the work of the principal investigator and asked the CRO Quintiles to investigate. The CRO reported that they could not find any discrepancies in the records of the clinical trials. Mortality among the study subjects continued; a total of 13 patients died.

Later, Quintiles found the same electrocardiograms (ECGs) in the charts of different patients, suggesting fraud. The CRO reported the situation to the hospital and to the Argentine authorities, and after a more thorough review the hospital dismissed the principal investigator. In June, 1998, the clinical trial was terminated at this particular site, and Hoechst discarded all information gathered for the GUARDIAN trial at the Naval Hospital. No problems were identified in any of the other study sites in Argentina. The principal investigator continued his private practice, and Hoechst did not request market authorization for a new indication for cariporide, to reduce the risk of death or new cardiovascular incidents, from the FDA (De Young and Nelson 2000).

An attorney reviewed the case, and concluded that at least three of the deaths that occurred during the clinical trial gave cause for prosecution. Following interviews with most of the patients and their families, the lawyer determined that 80 of the informed consent signatures were false. Patients who had signed the form stated that they did not know what they signed for. Clinical histories had been altered to show that patients met the study criteria for inclusion in the clinical trial, and several documents disappeared after the review began. The clinical trial protocols explain in detail how to manage participants, and the attorney questioned whether the research team had followed the protocol requirements or had ignored the study guidelines due to negligence, convenience or with the intention to commit fraud.

In 2010, the Criminal Court closed the case as it had passed the statute of limitations, and added that the investigation also had been defective (Espósito 2010):

> There is no evidence to show a causal link between the administration of the medication and the deaths. There is no medical expert's report, only pseudo expertise that could not show the responsibility of the defendants on the deaths

Causal relationships between participation in clinical trials and adverse effects, including deaths, are always difficult to establish. The case of cariporide in Argentina suggests that the difficulties in low- and medium-income countries may be even greater than in richer economies due to lack of experience and the slow pace of the judicial processes. Maybe the regulations should establish that all deaths of clinical trial participants should be investigated, and in case of doubt, autopsies should be obligatory.

The reasons why the violations of the Argentine regulations (lack of informed consent, fraud in the patient recruitment process, falsification of clinical records – infringements of good clinical practices) were not prosecuted and the professional license of the principal investigator was not withdrawn have not been explained.

4.4.3 The COMPAS Clinical Trial (GlaxoSmithKline GSK) in Santiago de Estero, Mendoza, and San Juan

The COMPAS clinical trial was conducted in the provinces of Cordoba (see Chap. 5), San Juan, Mendoza, and Santiago del Estero. The latter has the lowest

per capita income in the country – US$1,746 in 2005. San Juan province is also a poor province with a per capita income of US$2,800, against the national median in Argentina of US$4,700 (2005).

The province of Santiago del Estero had a population of just over 874,000 people in 2010, with approximately 250,000 living in the capital city, which is also named – Santiago del Estero. The Governor declared the vaccination with the experimental pneumococcal vaccine a Policy of the State. For this reason, physicians in the public facilities would recruit patients (Calvo 2007).

The financial compensation offered to the principal investigator was not disclosed, but for each baby recruited the sponsor paid US$350 and the clinical trial protocol asked for 4,500 babies to be recruited in Santiago del Estero (Calvo 2007). This would amount to more than US$1.5 million, a very large sum when compared with the per capita income of the inhabitants of the province, and especially taking into account that many of the services were supplied by the province.

The babies were recruited through the Eva Perón Children's Hospital, a public institution, and in the public primary care clinics and health centers located in the marginal neighborhoods in the City of Santiago del Estero. The people using these facilities had confidence in the physicians and recruitment was fast and easy; of all the parents who were invited to participate in the trial, only 14 declined (Calvo 2007). The physical conditions of the hospital, however, made it a poor choice for conducting clinical trials (Calvo 2007):

> [The hospital]... is now a prime example of how public medical care is deteriorating in Santiago del Estero: sick and healthy children share chemical toilets,[5] the main building has many unauthorized electrical connections, there are holes in the walls covered with cardboard, and tired old fans try to disperse the heat. They are not enough for the tide of worried mothers and crying children who daily pour into the hospital. To be able to conduct a clinical trial following international standards, the X-ray area was protected with lead and a freezer was provided

The regular outpatient workload for the four physicians working in the hospital was 300 daily patient visits. The clinical trial was added to this workload. A sign at the hospital entrance said: If you want to vaccinate your child for the first time, please present your identity card with that of your child. In 2008, the President of the Federation of Health Professionals in Argentina stated that (Seeger 2008):

> In Santiago del Estero recruitment was unethical, they recruited low-income women without telling them that their children would be part of a clinical trial, they made them sign without letting them read the informed consent, and added threats if they wanted to leave the study

This statement was supported by a physician from the Eva Perón Children's Hospital, who said: ... it was very unethical (Seeger 2008).

[5] Toilets that use chemicals instead of running water to sanitize fecal material, similar to the portable toilets used in construction sites.

Testimonials collected by an investigative journalist for the national newspaper Clarín found that one mother remembered the pressure and fear caused by the recruiters. One respondent who witnessed the consent process for her neighbor explained (Calvo 2007):

> . . . they read 13 pages to her because she could not read, and twice they said frightening words, such as deafness, mental retardation, or death

She thought that if she didn't offer her child to participate these things would happen to him; she did not realize that she was being warned about possible adverse effects. Both the principal and the co-principal investigators acknowledged that it was difficult to find suitable witnesses of the informed consent process, and that it was something that needed improvement.

A family member of one of the children who died in Santiago del Estero said (Federico 2008):

> There were mothers who were forced to sign when they were told that if they didn't their children would be taken by the police, treatment would not be given, or they wouldn't receive care

In all, 26 Latin American babies enrolled in the COMPAS trial, died; 12 in Argentina and the others in Panama and Colombia. Seven of the Argentine babies had been recruited in Santiago del Estero, while the other deaths occurred in the provinces of San Juan and Mendoza.

The Director of COMPAS in Latin America denied any relationship between the deaths and the vaccine. He affirmed that the babies participating in the clinical trial had lower mortality rates than the average infant mortality rate in their countries because the babies received continued medical follow-up and better medical treatment than the rest of the children in this age group.

GSK paid compensation to the families who lost their babies without accepting responsibility for the deaths. Subsequent inspections by ANMAT found that children did not receive the examinations specified in the protocol and that several children who had been hospitalized for acute respiratory infections were not excluded from the trial. Malnourished babies appeared to also have been recruited. This information was not included in the clinical trial documents, which is understandable if they were, in fact, violations of the inclusion/exclusion criteria.

The lack of communication between the regular hospital employees and the study personnel – as in the municipality of Cordoba (see Chap. 5) – may be another contributing factor to the death of some of the babies. A mother said (Seeger 2008):

> When we took the baby to the hospital with pneumonia - hours before the baby died - they said that they couldn't see us because the baby was in the study and we had to wait for the study physician. . .[and] no studies were done on the baby before he was enrolled in the trial

In response to the complaints about problems in Santiago del Estero made by physicians, families and the media, ANMAT reviewed the situation. In June and July of 2008, supported by Resolution 690 (Good Clinical Practices for Clinical Trials and Guidelines for the Inspection of Clinical Trials), an inspection was carried out by the ANMAT Chief of Inspections and two medical inspectors. They interviewed participants, physicians, and members of the clinical trial team,

and made home visits to participants to check the information received from other sources.

Using the results of the inspection report, ANMAT decided that in their next visit they would collect data about the community, to better understand the socio-economic context of the clinical trial. Subsequent inspections in the Provinces of San Juan and Mendoza, in October and December, respectively, included two sociologists in the inspection team. In the ensuing lawsuit, the two socio-medical reports were decisive for the judges. With the information obtained, ANMAT prepared a report and GSK ended the trial.

In June, 2009, ANMAT imposed a fine of 400,000 pesos (1US$ = 3.9 pesos) to GSK, and a fine of 300,000 pesos to each, the principal investigator and the co-investigator. ANMAT documented the following infractions:

- Non-compliance with the study inclusion criteria. The vaccine had been administered to patients with a history of acute respiratory infection; in several cases children had more than one hospitalization, which made them more susceptible to pneumococcal infections
- In the case of illiterate patients, the informed consent was not obtained in the presence of two witnesses
- Legal representation for signing the consent form was not established, neither at the beginning of the study nor during its implementation
- The documentation on the study participants was inaccurate; for example, their age and perinatal birth record were absent, and this information was necessary to evaluate whether the babies met the inclusion criteria
- There was no strategy to exclude from the study the babies who were carriers of HIV or had sickle cell disease or a history of splenectomy, since there are no reports that the appropriate tests were done to detect these illnesses

The defendants filed an action of unconstitutionality and on April 8, 2010, the national Judiciary's Office decided in favor of ANMAT (Poder Judicial de la Nación 2010).

In the court's decision, Articles 27 and following, the judges repeated the information presented in the ANMAT's socio-medical reports, and confirmed the double vulnerability of the population in which the vaccine was tested – as children, and from poor families. The Court said that the appellants (GSK and the researchers) (Poder Judicial de la Nación 2010:Art. 29):

> . . . had underestimated the Tribunal when they tried to say that the study participant population was not largely marginal nor from extremely low socio-economic circumstances

GSK and the sanctioned researchers had to know this, and it is in this light that judgment must take place since the two parties in this dispute have conflicting technical arguments (Art. 30). In Art. 31, the judges said:

> . . . Even if there is no real verification that the vaccine caused these deaths, and that the trial was a randomized, double blind study, the act of including these babies in a pharmacological trial only a few days after they had been hospitalized for various respiratory problems - pneumonia, bronchitis - demonstrates the appellant's [GSK and the researchers] responsibility for a serious violation of the legal rights of participants protected by regulation.

This was the first large fine nine by Argentinean standards imposed by ANMAT on a transnational company. Taking into account the wealth of GSK, the fine was symbolic. In 2011, the province of Mendoza also fined GSK for regulatory violations committed during the implementation of COMPAS in the state. The pharmaceutical company indicated that it would appeal the ruling. Eventually, GSK reversed the decision and paid the fine.

4.4.4 Complaints from the Braulio Moyano Neuropsychiatric Hospital for Women[6]

The Braulio Moyano Neuropsychiatric Hospital for Women was investigated by the National Ministry of Justice at the beginning of December, 2005, to ascertain if patients were participating in clinical trials without their consent. The investigation followed a request from the Secretary of Health of the City of Buenos Aires who had received complaints about irregularities occurring during the implementation of clinical trials at the Hospital (Clarín 2005a). The repercussions were immediate, and cross-accusations between the hospital administrators and the local health authorities about who was responsible for the regulatory violations followed.

According to the Secretary of Health, hospital physicians had said that clinical trials sponsored by Pfizer were being conducted without informed consent or patient signatures on consent forms. The multicenter study was testing drugs marketed for schizophrenia (olanzapine and ziprasidone) for non-approved uses (Clarín 2005b; Orchuela 2006; Federico 2006a).

Due to these complaints and to other problems, the hospital was placed under receivership by the Government of the City of Buenos Aires for a period of 180 days, and the Hospital Director, who had occupied his position for 21 years, was suspended (Rodríguez 2005). A hospital physician was appointed as official receiver and took over the administration of the hospital. At that time, the hospital had 1,100 patients, some of whom had been there for more than 40 years. Forty percent of the hospital was closed for repairs, aggravating patient overcrowding and questioning the wisdom of implementing clinical trials in such a setting (Página 12 2005).

The Secretary of Health of the City of Buenos Aires forwarded the complaints about the clinical trial to the federal court, and stated that the Hospital Director was responsible for conducting the trials without authorization, receiving US$5,000 per participant (Rodríguez 2005). The Secretary accused Pfizer of breaking the law by conducting clinical trials of medications without authorization and without the

[6] This case study is based on Orchuela (2006).

patients' signatures. In the words of the Secretary (Federico 2006a cited in Orchuela 2006)[7]:

> The question which has been raised and is being investigated by the Court, is whether these patients, who are poor, had been deprived of their liberty and sent to the hospital by a Court order, had problems due to their cultural level and difficulties in understanding certain concepts, had been coerced into signing the informed consent, as if they had the ability and the freedom to make personal decisions. These people [the physicians who conducted the clinical trial], who enjoy a very high professional status, had to know that these patients did not have full use of their mental faculties

The Chief of Teaching and Research for the Hospital who was responsible for coordinating clinical trials stated that (Federico 2006a cited in Orchuela 2006):

> . . . all the patients gave informed consent, as they were not and are not insane in the legal sense, as they did not have a judgment of insanity. Although detained in a psychiatric system, a person may sign. This concept is international. This consent is always accompanied by that of a relative, as well as the presence of a witness. This is routine in any research protocol

This Hospital Chief of Teaching and Research underlined the political dimension of the accusations by saying that those physicians who complained had previously authorized the clinical trials (Clarín 2005a), and that the Director of Mental Health of the City of Buenos Aires had approved the clinical trials when he was not only the Director but also a member of the Hospital Committee for Teaching and Research (Pachamé 2006). In reality, the problem was not the protocol, but with its implementation – in this case, the lack of informed consent from vulnerable patients.

The suspended Hospital Director stated that Pfizer had fullfilled all the requirements and the Chief of Teaching and Research confirmed that the medications were approved and could be obtained in any pharmacy in the city, insinuating that the study was not a clinical trial. This explanation is similar to the response offered by the oncologist, which was discussed earlier. The Chief of Teaching and Research added that the protocol had the required approvals and authorizations from ANMAT, the Independent Ethics Committee, and the Secretariat of Health (Federico 2006b).

The case of the Neuropsychiatric Hospital triggered public debate and uncovered problems in other hospitals in Buenos Aires (to be discussed later), leading some observers to conclude that the rights of patients were violated in a generalized way, even if the studies had been approved by the institutional RECs (Pachamé 2006).

The case is an example of the difficulties of the Argentine Justice system to rule when during the process of implementing clinical trials the existing regulations or

[7] Title 10 of the Civil Code (Of the demented and incompetent) says that: No person will be termed demented, as defined by this Law, unless the dementia is previously verified and declared by a qualified Judge (Art. 140); Persons who, because of mental illnesses, are not able to care for themselves or their property, will be pronounced incompetent by reason of dementia (Art. 141); The Judicial declaration of dementia may be provided only upon request, following a medical examination (Art. 142).

the human rights of the participants are violated. In this case, as in many others, justice has not been sustained, not only because of the lack of sanctions, but also because three years later (2009) the Chief of Teaching and Research of the Neuropsychiatric Hospital, who had coordinated the clinical trial, was appointed Director of the Hospital by the new Secretary of Health of the City of Buenos Aires.

4.4.5 Polyclinic PAMI II de Rosario[8]

PAMI is the national integrated healthcare program for pensioners and retirees. Between 2004 and 2005, Wyeth financed a multicenter clinical trial involving an antibiotic, tigecycline, which was being tested for treatment of pneumonias acquired during hospitalization (nosocomial pneumonias). The study was conducted in six facilities in Argentina, one of which was the Polyclinic PAMI II of Rosario (third largest city in Argentina) and the remaining five located in Buenos Aires were non-PAMI facilities. In the Polyclinic of Rosario there were nine participants and the principal investigator received US$40,790. Wyeth paid this amount directly to the Polyclinic and not to the national headquarters of PAMI (Weinfeld 2007). According to the National Director of PAMI the funding was not used to compensate PAMI for the infrastructure and all consumables used for the trial.

This case is particularly interesting because shows contradictions in the information provided by PAMI and ANMAT. According to PAMI's regulations, clinical trials conducted in its facilities need to be approved by the national office. The PAMI national office did not know that the trial was taking place in Rosario until two anonymous communications alerted the national authorities about the trial. In this case, not even the institutional REC had approved the trial. In preparing the Administrative Inquiry, PAMI's Legal Office of Research of Punishable Internal Offenses (*Unidad Fiscal de Investigación de Delitos Cometidos*) asked ANMAT if it had authorized the trial and three times received communications affirming that it had not.

However, when gathering cautionary measures (*medidas cautelares*) ANMAT found an authorization, and claimed that it always had existed. According to ANMAT, a REC had approved the clinical trial and the director of the polyclinic was aware of it (Boletín Fármacos 2007). PAMI's national headquarters then discovered that the REC that approved the trial was not the institutional REC but an ad hoc external REC for this trial. The Director of ANMAT said that (Boletín Fármacos 2007):

> . . . he could not believe that in a public hospital, physicians could carry out clinical trials on their own

[8] PAMI is the Integrated Health Service which is part of the National Institute of Social Services for Retirees and Pensioners.

In addition to the contradictory responses of ANMAT (which should remind the reader of the remark about the indolence of ANMAT made by the Ombudsman who investigated the oncological trials discussed above), there were serious allegations about problems with the informed consent. The informed consent form consisted of 18 densely packed pages of difficult reading, making it (Weinfeld 2007):

> . . . almost impossible for the average patient in a geriatric hospital to analyze and understand this incomprehensible document. If the elderly patient is in addition sick with pneumonia the likelihood of understanding it is almost nonexistent. Most likely, they sign the document without having understood it. These were vulnerable patients, which raises additional questions on the consent form

The Legal Department responsible for investigating infractions within PAMI presented the case in Federal Court and both the principal investigator and the Director of the hospital were dismissed from the polyclinic (Weinfeld 2007).

4.5 Conflicts of Interest Within ANMAT

Conflicts of interests are common within the regulatory agencies themselves – as documented for the FDA (Lenzer 2004; Union of Concerned Scientists 2011).

The following case presents a conflict of interest within ANMAT. In 2010, two persons who had positions in the Argentine Institute for Evidence Based Medicine (IAMBE) – founded in 1997 – and who simultaneously worked for ANMAT were promoted to senior positions; one became the Director of one of the five Departments within ANMAT, namely the Department of Planning and Institutional Relations.

According to its web page, IAMBE has conducted five clinical trials sponsored by foreign universities and other agencies rather than the pharmaceutical industry, but the studies still required ANMAT authorization. In one study (The Magpie Trial: MAGnesium Sulfate for Prevention of Eclampsia – comparing magnesium sulfate with a placebo), the name of one of the Argentine clinical trial leaders who is at present (2012) the Director of Planning at ANMAT appeared on the informed consent document as the contact for the Magpie Coordinating Office in Latin America, and he listed his ANMAT e-mail address. In other words, the same person appeared to be representing the study sponsor and ANMAT – which authorized the study.

The appearance of a potential conflict of interest for an individual does not mean that rules were violated or personal gain was involved, only that there is the potential for this to happen. It is precisely to avoid these situations that institutions should have strict controls to preclude potential conflicts of interests.

In 2004, IAMBE signed a memorandum of cooperation with CEDPAP, based on "the coincidence of purpose in the objectives of both parties" (IAMBE not dated). As noted in the COMPAS clinical trial and in Chap. 5, CEDPAP was not known for following internationally accepted ethical principles. IAMBE is a consultant to the pharmaceutical industry, which is another reason why people having

important responsibilities within IAMBE should not simultaneously have administrative responsibilities at ANMAT.

4.6 Conclusions

Over the course of the years, Argentina has advanced in the development of clinical trials regulation. We have seen that on several occasions there have been regressions and that the country does not have a national law that regulates clinical research with humans. We have discussed issues regarding the limitations of informed consent, as it is been implemented, and problems related to the slow pace of the judicial system. This chapter has also presented clinical trials that violated internationally accepted ethical principles that were discovered after tragic events and by concerned citizens, including investigative reporters, and by Administrative Summaries or the courts. We do not know how many other trials have similar or other ethical problems and have gone undetected. The lack of transparency and the secretive behavior that characterizes clinical trials make it impossible to have a better understanding of the situation.

The global pharmaceutical industry and local partners in clinical trials contribute to the problems discussed. In Argentina, two private ethics committees, not affiliated to medical care institutions, are responsible for the ethical approval and the monitoring of almost 80 % of all clinical trial protocols, and make a profit from this activity. The approval of protocols has become a good business. We have presented some evidence of the conflict of interests that such a system generates and the reasons to doubt the impartial evaluation of protocols.

This chapter has documented that, by local economic standards, principal investigators receive a high compensation per subject recruited. While it could be argued that principal investigators incur in expenses during the implementation of a trial, it has been shown that they and many of their staff continue to be in the payroll of public or private institutions, and frequently all or part of the overheads incurred during the trial are assumed by the institutions. When the economic interests of local collaborators are affected by the regulations, they will exercise pressure on the public institutions to regress or overlook infractions. Their pressures together with those exercised by the powerful pharmaceutical industries create an insurmountable barrier for the protection of participants, most of whom are poor citizens.

The case studies discussed show that most participants are persons of limited resources or are vulnerable, as is the case of children and the elderly. It is generally accepted that inducements to recruit participants, which in the case of Argentina could include providing access to unaffordable medicines or better medical care, are considered unethical. Negative inducements, that is, when potential participants fear that the refusal to accept the attending physician's request to participate in a trial may have negative consequence for future care, is also a violation of ethical principles.

From the information presented, it can be concluded that with few exceptions, the approval of protocols by institutional or private RECs does not protect the human rights of participants. Potential conflicts of interests seem to be common among members of RECs. By and large, the approval is an administrative act, there are no assurances that the consent given is informed, and the limited monitoring of the implementation process is insufficient to detect errors in data entry, the manipulation of data or the undue retention of patients, or to ensure that adequate treatment is provided to patients who become sick. All these are issues that have an impact on the quality of the data. We would like to suggest that there is a need to have a national ethics committee with capacity to recruit specialists in the different medical fields to review the protocols in their area of expertise. Members should be free of conflicts of interests. A national committee does not exclude the institutional RECs that would have to evaluate if the trial is pertinent for an institution and if they will be able to protect the human rights of participants.

The Ministry of Health and ANMAT could be more forceful in demanding adherence to existing regulations in order to protect the integrity of the clinical trials and the human rights of the participants. The abundant information obtained from the reviews of the trials presented, particularly from the cancer studies, shows that internal conflicts within the agency preclude adherence to existing regulations and that, with rare exceptions, throughout its 20 years of history, has not been willing to promote transparency, and has been overcome by inefficiencies.

Regulation 6677 does not require the RECs to know and consequently review the budgets of clinical trials. The deletion of this responsibility was a step back. It is important for the RECs to study the budget because:

- The size of the payments by the sponsor to the principal investigator and to physicians, per patient recruited, may impact the integrity of both the recruitment and informed consent process, and lead the recruiters to disregard inclusion/exclusion criteria for study participants
- If payment is based on the number of patients who remain until the end of the study, it can result in unjustified patient retention, including putting patients at excessive risk
- It can be used to determine if adequate funds are allocated to cover the overhead costs of the trial
- It is necessary to verify that there are enough funds to monitor the implementation of the trial
- Per diems and other compensations to participants need to be assessed to ensure that they are not inflated or constitute an inappropriate inducement to participate

The registry of clinical trials that has been implemented does not fulfill the requirements of Resolution 102. In addition to broadening the required fields of information, it would be important to include protocols that have been rejected, and the reasons for the rejection. This information could assist other RECs to re-evaluate their decisions. Other countries would also benefit from knowing that a protocol has been rejected. When a protocol is rejected in a country, the pharmaceutical industry seeks to conduct the studies in other countries with less safeguards

for the approval of trials; the literature has named these countries "savior countries" (Bartlett and Steele 2011).

We have shown that in some cases the quality of data gathered was compromised due to falsifications and manipulation of data, by failures to follow exclusion/inclusion of criteria, and by participants' low understanding of the experimental nature of the trial. We do not know if the failures that we have detailed from the limited information available are the rule or the exception. The possibility that these and other failures not detected in our study occur more frequently than imagined means that regulatory agencies that used data obtained in Argentina to approve the commercialization of the tested product may place consumers at risk. This is a thought, that given the information that has been presented, political leaders need to ponder.

In the end, it will be the Argentine political leaders who need to decide if they want to protect their citizens, or if they prefer to accept the conditions of an industry that in the United States has a public approval rate lower than that of the tobacco industry. They must also decide if they wish to require ANMAT to protect clinical trial participants and the quality of the data, or let the regulatory agency continue to have a lethargic approach to violations of regulations and of ethical principles.

Annex 4.1: Legislation Governing Clinical Trials in Argentina

Legislation	Year	Observations
Establishment of ANMAT by Decree 1490	1992	
ANMAT Regulation 4854	1996	Adopts guidelines for clinical pharmacology studies
ANMAT Regulation 5330	1997	Approves the rules of good practices for research in clinical pharmacology studies http://www.anmat.gov.ar/webanmat/NORMATIVA/NORMATIVA/MEDICAMENTOS/DISPOSICION_ANMAT_5330-1997.PDF Accessed 2 Nov 2012
ANMAT Regulation 690	2005	Approves the guide to inspections for clinical investigators http://www.sac.org.ar/files/files/disposicion_anmat_690_2005.pdf Accessed Nov 2 2012
Ministry of Public Health for the Nation, Resolution 1490	2007	Guide to good clinical practice in human beings, taking into account Nuremberg, Helsinki (version 2004), WHO (2000), CIOMS (2002), and Nuffield (Council of Bioethics (2004)

(continued)

(continued)

Legislation	Year	Observations
		http://www.anmat.gov.ar/webanmat/Legislacion/Medicamentos/Resolucion_1490-2007.pdf Accessed 2 Nov 2012
ANMAT Regulation 6550	2008	On Ethics Committees and Informed Consent http://www.reumatologia.org.ar/userfiles/file/investigacion-farmaco-clinica/ANMAT-6550-08.pdf. Accessed 2 Nov 2012
ANMAT Regulation 1067	2008	Establishes a new form for reporting of RAMSI (serious and unexpected adverse drug reactions). Accessed 2 Nov 2012 http://www.infoleg.gov.ar/infolegInternet/anexos/135000-139999/138239/norma.htm. Accessed 2 Nov 2012
Ministry of Public Health for the Nation, Resolution 102/09	2009	Establishes the register of clinical trials in human beings http://www.anmat.gov.ar/webanmat/Legislacion/Medicamentos/Resolucion_102-2009.pdf. Accessed 2 Nov 2012
ANMAT Regulation 6677/10	2010	Good clinical practice regime for clinical pharmacology studies http://www.anmat.gov.ar/webanmat/Legislacion/Medicamentos/Dispo_6677-10.pdf. Accessed 2 Nov 2012
Ministry of Justice of the Nation, National Directorate for Personal Data Protection. Law 25.326 / 00	2000	The purpose of the Act is to protect "personal information in files, records, databases, or other technical methods of data processing, whether public or private for use in reports, to ensure the right for respect and individual privacy, and also access to any other personal information, in accordance with the provisions of Article 43, third paragraph of the National Constitution." http://www.infoleg.gov.ar/infolegInternet/anexos/60000-64999/64790/norma.htm. Accessed 2 Nov 2012

http://www.anmat.gov.ar/webanmat/normativas_medicamentos_cuerpo.asp

References

Bartlett, D.L., and J.B. Steele. 2011. Deadly medicines. *Vanity Fair*. http://www.vanityfair.com/politics/features/2011/01/deadly-medicine-201101. Accessed 31 Oct 2012.

Boletín Fármacos. 2007. Pruebas controvertidas con medicamentos en PAMI y proyectos de ley que intentan cubrir vacíos legales (Contested drug trials at PAMI and bills that try to fill a legal

vacuum). *Boletín Fármacos* 10(4): 54–55. http://www.saludyfarmacos.org/boletin-farmacos/boletines/sep2007/etica-y-derecho/. Accessed 25 Sept 2012.

Calvo, P. 2007. Santiago: cuestionan la captación de niños para ensayos de vacuna (Santiago: It is questioned the enrollment of children in vaccine trials). *Clarín*. 23 Dec. http://edant.clarin.com/suplementos/zona/2007/12/23/z-04015.htm. Accessed Oct 31 2012.

Clarín. 2005a. Graves acusaciones cruzadas tras la intervención en el Moyano (Serious crossed accusations after Hospital Moyano is placed under receivership). 22 Dec. http://edant.clarin.com/diario/2005/12/22/laciudad/h-07001.htm. Accessed 25 Sept 2012.

Clarín. 2005b. Allanan el Hospital Moyano (Hospital Moyano placed under receivership). 2 Dec. http://edant.clarin.com/diario/2005/12/02/laciudad/h-05502.htm. Accessed 25 Sept 2012.

Clarín. 2007. Tras la muerte de un paciente en el Hospital Fernández (After the death of a patient at the Hospital Fernández). 5 Dec. http://edant.clarin.com/diario/2007/12/05/sociedad/s-03601.htm. Accessed 25 Sept 2012.

De Young, K., and D. Nelson. 2000. Latin America is ripe for trials and fraud. *The Washington Post*. 21 Dec, p. A01.

Espósito, N. 2010. Cierran una causa que investigaba experimentos en el Hospital Naval (A court case that investigated clinical experiments at the Hospital Naval is terminated). Tiempo Argentino, 7 Aug. http://tiempo.infonews.com/2010/08/07/argentina-3991-cierran-una-causa-que-investigaba-experimentos-en-el-hospital-naval.php. Accessed 31 Oct 2012.

Federico, M. 2006a. Negocios, mentiras y la interna del mundo "psi" (Businesses, lies and the patient at the psychiatric ward). El Médico del Conurbano 187, 3 Mar.

Federico, M. 2006b. Lo que está en juego es la salud de la población, Pablo Berretoni, Director General de Salud Mental del GCBA (What is in play is the health of the population says Pablo Berretoni, General Director of mental health of the city of Buenos Aires). El Médico del Conurbano 187, 3 Mar.

Federico, M. 2008. Se investiga si 12 bebés murieron por un experimento (It is investigated the possible connection between the cause of death of 12 babies and their participation in a clinical trial). *Crítica de la Argentina*, 10 Jul. http://criticadigital.com/impresa/index.php?secc=nota&nid=7769. Accessed 31 Oct 2012.

FEFyM. 2010. Seguimiento de Protocolos. Informe Periodo 2009 (Looking at protocols. Report for 2009). Buenos Aires. http://fefym.org.ar/novedades/auditorias_2009.pdf. Accessed 31 Oct 2012.

Gonorazky, S.E. 2008. Comités de ética independientes para la investigación clínica en Argentina Evaluación y sistema para garantizar su independencia (Independent ethics committees for clinical research. Evaluation and a system to guarantee independence). *Medicina (Argentina)* 68: 113–119.

IAMBE. No date. Convenios (Agreements). http://www.iambe.org.ar/relac_inst.htm. Accessed 31 Oct 2012.

Interview. 2003. Entrevista con el jefe de servicios de farmacia de un hospital del conurbano de la Ciudad de Buenos Aires (Interview with a the head of the department of pharmacy of a hospital in Buenos Aires). 14 Sept.

Lenzer, J. 2004. FDA is incapable of protecting US "against another Vioxx." *BMJ* November 27; 329(7477):1253. doi: 10.1136/bmj.329.7477.1253. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC534432/. Accessed 31 Oct 2012.

Lipcovich, P. 2010. Definiciones del experto Juan Carlos Tealdi durante el Congreso de Bioética y DD.HH. del Mercosur. "Es y debe ser una disciplina comunitaria" (Definitions by expert Juan Carlos Tealdi during the Bioethics and Human Rights Congress of Mercosur. It is and should be a communitarian discipline). *Página* 12, 9 Dec. http://www.pagina12.com.ar/imprimir/diario/sociedad/3-158362-2010-12-09.html. Accessed 31 Oct 2012.

Mondino, E. 2003. Informe especial sobre ética en la experimentación con humanos y el deber del estado nacional. Defensoría del Pueblo de la Nación, Buenos Aires (Special report about ethics in experimentation in humans and the duty of the Nation). http://www.unal.edu.co/bioetica/documentos/cd_ei_sh_a1_inf_ex_sh_arg_05.pdf. Accessed 31 Oct 2012.

Orchuela, J. 2006. Denuncias por investigación de medicamentos sin consentimiento en hospital neuropsiquiátrico de mujeres (Claims caused by clinical trials without consent at the women's psychiatric hospital). *Boletín Fármacos* 9(2): 126–129. http://www.saludyfarmacos.org/boletin-farmacos/boletines/abr2006/etica-y-medicamentos/. Accessed 2 Nov 2012.

Pachamé, J. 2006. Neuropsiquíatricos, desmanicomialización o negocio capitalista (Neuropsichiatric centers, outpatient treatment or a capitalist business). *Tribuna de Salud*. http://www.tribunadesalud.com.ar/node/26. Accessed 2 Nov 2012.

Página 12. 2005. Electroshock en el hospital Moyano [Electroshock at the Hospital Moyano]. Dec 21. http://www.pagina12.com.ar/diario/sociedad/3-60771-2005-12-21.html. Accessed Nov 2 2012.

Peralta Corneille, A. 2009. Bioethics education in Latin America and Caribbean. Presentation at the UNESCO International Bioethics Committee Sixteenth Session. Mexico City. 23 Nov. http://www.unesco.org/new/fileadmin/MULTIMEDIA/HQ/SHS/pdf/peralta_latin_america.pdf. Accessed 24 Sept 2012.

Pérez, A. 2008. Clinical trials in Argentina. 10 years of experience. ANMAT, Buenos Aires (powerpoint).

Poder Judicial de la Nación. 2010. Caso número 13.617, ANMAT C/GlaxoSmithKline, Argentina SAM y otros S/INF Ley 16.463 firmado por el juez Alejandro J. Catania (Case no 13,617, ANMAT/GlaxoSmithKline, Argentina SAM and others S/INF Law 16,463 signed by judge Alejando J. Catania). Buenos Aires, 8 Apr.

Quiñones, V.H. 2010. *Encuesta anual de investigación clínica* (Annual Survey of Clinical Research). Buenos Aires: CAEMe.

Rodríguez, C. 2005. *Las internas del Moyano, como conejillos de Indias* (The intern women of Moyano are guinea pigs). *Página 12*, 22 Dec. http://www.pagina12.com.ar/diario/sociedad/3-60799-2005-12-22.html. Accessed 2 Nov 2012.

Savoia, C. 2007. Los riesgos de la medicina; la vigilancia del estado a la investigación científica (The risks of medicine; keeping vigilance of the condition of scientific research). *Clarín*, 10 Dec Section Actualidad.

Seeger, M. 2008. Faltan morir 13.986 bebés. Argentina de espaldas a una aberración (Still 13,983 babies to die. Argentina avoids confronting an outrage). *Agencia Efe*, 14 Aug. http://www.igooh.com/notas/faltan-morir-13-986-bebes/. Accessed 2 Nov 2012.

Union of Concern Scientists. 2011. (FDA) Scientist survey shows progress, but problems remain. http://www.ucsusa.org/scientific_integrity/abuses_of_science/fda-survey-shows-progress.html. Accessed 2 Nov 2012.

Vidal, S. 2004. Acerca de la independencia de los Comités de Ética de la Investigación (About the independence of research ethics committees). *Special issue of Bioética* 5: 51–58. http://www.toposytropos.com.ar/N7/bioetica/bioetica10.htm. Accessed 2 Nov 2012.

Weinfeld, M. 2007. Cobayos de tercera edad para una prueba ilegal (Elderly guinea pigs in an ilegal trial). *Página* 12, 26 Mar. http://www.pagina12.com.ar/diario/elpais/1-82337-2007-03-26.html. Accessed 2 Nov 2010.

Young, G. 2007. Dos de cada tres ensayos clínicos no están registrados [Two of every three clinical trials are not registered]. *Clarín* 9. Dec 9, Section Actualidad. http://www.llave.connmed.com.ar/portalnoticias_vernoticia.php?codigonoticia=13933. Accessed 2 Nov 2012.

Chapter 5
Politics and Clinical Trials in the Province of Cordoba

Antonio Ugalde and Nuria Homedes

5.1 The Clinical Trial Regulatory Framework in Cordoba

As explained in Chap. 4, Argentina is a federation of 23 provinces and the autonomous Federal Capital. Each province has its own executive, legislative, and judicial governments. Each province has its own Ministry of Health that is responsible for the regulation of the health sector and the provision of medical care services for the poor.

It is estimated that one third of all clinical trials conducted in the country take place in the Province of Cordoba, which houses about one tenth of the national population (Fernández 2005a). Recognizing this situation, the provincial government initiated the development of standards for clinical research involving humans. In 2001, the bioethics department of the provincial Ministry of Health designed a program for ethics in health research, which included the creation of a Provincial Commission for Ethics in Health Research (COPEIS in Spanish) to develop ethical standards, train professionals in research ethics, establish criteria for accreditation of Institutional Research Ethics Committees (IRECs), create a Provincial Registry for Health Research (RHR), and evaluate research protocols that could threaten the wellbeing of clinical trial participants.

During the first two years (2001 and 2002), almost 200 professionals were trained in five-month classroom courses. The COPEIS started functioning in 2002 as part of a supervision unit of the provincial Ministry of Public Health, a status that

The authors would like to thank Juan Carlos Tealdi and Susana Vidal for their assistance and comments during the preparation of this chapter. The authors have sole responsibility for analysis and interpretation of the data.

A. Ugalde
Department of Sociology, University of Texas, Austin, TX, USA

N. Homedes (✉)
School of Public Health, Division of Management Policy and Community Health, University of Texas Houston Health Science Center, El Paso, TX, USA
e-mail: nhomedes@utep.edu

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_5,

gave it legitimacy and sanctioning powers. The beginning of the following year (2003) saw the approval of Ministerial Resolution 729/02, which included the criteria for accreditation of the IRECs and the model for the evaluation of research protocols. Only hospital-based IRECs would be accredited; ethics committees in non-hospital settings, such as those established by foundations or other research centers, would not be accredited in the Province of Cordoba, although they could be accredited in other parts of the country. At the end of 2003, 11 IRECs had been accredited in the Province, and the RHR was operational (Vidal 2006).

Parts of the legislation – including the functions of the COPEIS and the decision to accredit only hospital-based IRECs – was rejected by researchers interested in conducting clinical trials at private centers and foundations, although highly complex private institutions had no problem accommodating to the new regulations (Ministerio de Salud 2006). The disagreement and rejection of these legislative items created difficulties for the staff in the bioethics department who had developed the standards (Ministerio de Salud 2006).

In an attempt to overcome these problems and the pressure from the private centers, the bioethics unit strengthened and increased the trainings for researchers and other personnel, especially those responsible for implementing the regulation and evaluating the clinical trials. Biomedical research institutions and human rights organizations had always been invited to designate representatives to the COPEIS, and information on the relationship between research involving humans and human rights was shared with the public. The promotion of civic participation and democratic inclusion was intended to strengthen the project.

Researchers working in small private centers organized and requested the political authorities of the Province to remove the regulatory aspects that interfered with the implementation of clinical trials. Without consulting either the experts in bioethics of the Provincial Ministry of Health, or the COPEIS, the clause in Resolution 729 requiring submission of clinical trial budgets and financing to the IRECs before the approval of a clinical trial, was suspended – just three months after it had become effective. Specifically, information was no longer required regarding: (1) the detailed research budget (the amount paid by the study sponsor, generally a multinational pharmaceutical company, to the principal investigator and to other researchers and institutions); (2) the compensation promised to the study participants (including expenses and access to medical attention); and (3) where appropriate, the fee to be paid to an institution for the evaluation of the study protocol by its IREC. The economic aspects of clinical trials have an important relationship with ethics and respect for the human rights of the participants, which is not always recognized by researchers, including those in the USA (Barlett and Steele 2011).

In October 2003, the Provincial authorities suspended the activities of the COPEIS, and in November, the agency was eliminated. New standards were published keeping much of the original content, but removing the requirements to: (1) name the place where the clinical trial participants would receive health care and the referral center where they could go in case of need; (2) provide insurance to compensate participants in case of harm attributable to their participation in the clinical trial; (3) describe the mechanisms to ensure access to treatment following the completion of the clinical trial; and (4) provide the budgetary information

previously noted - payments to researchers, participants, and institutions. In addition, the new standards allowed accreditation of IRECs in research centers without medical care services.

Instead of the disbanded COPEIS, a Provincial Commission for Research with Human Subjects (CPISH in Spanish) was created. The new Commission consisting of three researchers from the private sector and one expert in bioethics started operations in 2004, but the bioethics expert resigned, soon after, and the Commission continued for some time without a bioethicist, until the position was replaced with a clinical researcher. In a very short time, the new Commission approved 14 IRECs, more than the previous Commission had approved in its two years of existence. Of the 25 approved IRECs, 18 were in private institutions, of which seven were highly complex institutions, five were of medium or low complexity, and six were centers, foundations, institutes, or polyclinics. The remaining seven IRECs were in public institutions, all highly specialized referral centers (Ministerio de Salud 2006).

The Provincial Ministry of Health continued to gather data on the protocols approved by the IRECs, such as the number of participants, the date of completion of the study, and adverse events. The information on the clinical trials authorized in the Province and the institutions where they were implemented became available on the internet, but the training program established by the old Commission was suspended.

Also in 2004, the researchers opposed to Resolution 729 established the Clinical Research Society of Cordoba (SICC in Spanish) in the city of Cordoba, which has been joined by many clinics, health centers, institutes, foundations, and private, and some public, hospitals. Little information about their activities is available on their web page: (http://www.sicc.org.ar/sicc/index.php).

In 2010, the SICC, together with the Argentine Chamber of Clinical Research Organizations (CAOIC in Spanish), organized a modular program for training and certification in clinical research. The first module of the program, a one-day intensive course, took place in December 2010, with almost 100 researchers in attendance. This is the only activity mentioned on the Society's web page, suggesting that it functions primarily as a pressure group. Training in clinical research – in this case, clinical trials outside the academic environment and in private institutions with economic connections to the pharmaceutical industry – might be tainted with conflicts of interests.

An investigative journalist, reviewing the minutes of the CPISH, identified conflicts of interest in almost half of the 78 meetings held by the Commission during 2005. A substantial number of evaluators had conflicts of interest and could not participate in meetings, which had consequences. In some cases protocol approvals were granted in the absence of quorum, and with the presence of only one or two persons (Fernández 2005b).

Following the appointment of a new Provincial Minister of Health towards the end of 2006, the Ministerial Resolution 493/2006 was passed, leading to the suspension of the CPISH. The authorization of clinical trials did not resume until January 17, 2007. In an interview with the press, the Minister said (Fernández 2006):

> There is a huge number of research proposals in the review process, and we prefer to wait until the new standards are ready. Approvals had been granted at a rate of three to four protocols per week [meaning that previously the protocols had been reviewed too expeditiously]

When all the members of the Commission were asked to resign, the Minister temporarily assumed its functions. According to statements to the press, this was necessary to avoid possible conflicts of interest – a criticism raised against former Commission members, all of whom were clinical researchers. Resolution 22/07, published on January 24, 2007, provided the new standards for biomedical research involving humans (Boletín Oficial 2007), which aimed at increasing transparency and avoiding conflicts of interest during the clinical trial approval process. Referring to criticisms (see below), the Minister said (Fernández 2006):

> We do not want to recruit patients in the public sector for studies that will be conducted in the private sector

Regulation 22/07 rescinded several clauses introduced by the previous Minister, revived others included in Resolution 729 that had generated opposition, and added a few new clauses. The CPISH was replaced by the Health Research Ethics Review Board (COIES in Spanish), which remains the governing body for clinical trials. Much of Resolution 22/07 discusses the IRECs, and mandates the inclusion of five permanent members: one with experience in research, another with experience in bioethics, a community representative, a non-physician health professional, and a legal advisor. The composition of the new IREC is very different from its predecessor, and, if needed, the IRECs can invite specialists to provide expert opinions.

For clinical trials to be conducted in the public sector, Resolution 22/07 established three IRECs: one for clinical trials in maternal-child health (probably in response to a situation which will be presented later in this chapter), another for clinical trials related to mental health, and the third for all other protocols. The IRECs were given clear responsibility for all necessary follow-up during the implementation of the clinical trials.

Collecting a percentage of the proposed research budget from researchers or sponsors was one innovation introduced by Resolution 22/07. The percentage differed for public and private institutions. The funds raised would cover the costs of monitoring the study, and other items such as the Provincial Registry of Health Research.

Annex III of the resolution indicates that the requests for protocol evaluation had to include a fee to be paid to the institution of the IREC that would be conducting the evaluation. It did not establish the method to determine the amount of the fee, nor did it state allocation of the fee to the different tasks.

The exclusion of institutions without medical care services was reinstated. However, a few months later it was amended. Specialized private institutions without medical care services could request an exception and be allowed to establish an IREC (Gobierno de Córdoba 2007):

> . . . to evaluate and control only ambulatory studies related to the specialty of the health facility

The new amendment also required indemnity insurance in case of disability or death caused by participation in the clinical trial.

Resolution 22/07 did not require a detailed budget for the proposed clinical trial, only a declaration from the principal investigator showing the compensations payable to the participants for their expenses and for necessary medical attention. Only healthy participants could receive payment.

5.2 Clinical Trials in the Children's Hospital of the Municipality of Cordoba

The medical facilities of the Municipality of Cordoba, which serve the poor and the indigent, have been used to recruit and conduct clinical trials since 1987. The Municipal Children's Hospital is a high technology hospital and serves as referral center for many primary care centers (Ávila Vázquez 2007).

According to the National Administration of Food, Drugs and Medical Technology (ANMAT in Spanish), between 1996 and 2003, 19 clinical trials were conducted at the Children's Hospital, and the Chief of the Department of Pediatrics, who supervised 50 pediatric residents, was listed as principal investigator for 16 of the 19 studies (Municipalidad de Córdoba 2006).

Most of these studies were Phase III trials of vaccines, antibiotics, antihypertensives and asthma medications for children, and were sponsored by SmithKlineBeecham, Merck, Sharp & Dome, Upjohn, and Aventis, among others (Municipalidad de Córdoba 2007). ANMAT did not share information on the results of the trials, serious adverse events and deaths, or agreements between the principal investigator and the sponsors of these studies with the Municipality (Municipalidad de Córdoba 2006). ANMAT did not provide information about the number of trial participants to be recruited in the province, but information collected from municipal institutions indicated that 2,200 children were participating in the trials directed by the Chief of Pediatrics (Municipalidad de Córdoba 2007:4). Ávila Vázquez (2007) estimated that the researchers could have received between US$500 and US$12,000 per patient recruited, and the total amount collected by the researchers could be up to US$ 24 million. Most of these studies took place through the Center for Studies for the Development of Advanced Projects in Pediatrics (CEDPAP in Spanish), a private organization (CRO) directed by the Chief of Pediatrics of the Children Municipal Hospital, who implemented clinical trials in this hospital and in other public sector facilities.

In 1998, CEDPAP signed a three-year contract with the Municipality of Cordoba. The contract was for the surveillance of pneumococcus infections and read (Sarasqueta 2004:34):

> . . . given its future importance for the development of interventions to reduce respiratory infections in children all departments of the Ministry of Public Health and Environment of the Municipality of Cordoba are authorized to participate in this project. . .

CEDPAP's interest in preparing the ground for future vaccine trials was clear from the language included in the contract.

CEDPAP's administrative offices were located inside the Children's Hospital until 2001. The fact that the Department of Pediatrics and CEDPAP were headed by the same physician, had the same postal address and all documents related to the clinical trials had the logos of the two institutions was a cause of confusion; and hospital staff and outside researchers worked side by side. Hospital staff resented the fact the clinical trials benefitted businesses, and the public hospital was not compensated for the use of supplies and human resources. However, it was not until 2006 that CEDPAP's director was prosecuted for allowing a private business to benefit from the resources of a public hospital.

After the CEDPAP offices were moved from the Hospital, the clinical trials continued to be conducted inside the hospital, and the relationship between the hospital and CEDPAP was well explained by the hospital's director in a memorandum to the Directors of the Departments of Pediatrics, Surgery and Diagnosis and Treatment, where he stated that CEDPAP would continue to be the "Research Branch of our hospital" (Municipalidad de Córdoba 2006:4).

The Chief of Pediatrics continued implementing clinical trials in the municipal hospital after the three-years contract expired. During his work as principal investigator of clinical trials, he achieved prestige among his peers and the recognition of international institutions, allowing him to establish connections with provincial and national politicians. CEDPAP also gained recognition, and signed contracts with Argentinean universities and municipalities to carry out other research projects.

In 2003, two years after the expiration of the contract, CEDPAP signed a Cooperation Agreement with the Municipality of Cordoba. The Annex to the Agreement clarified that CEDPAP wanted to conduct clinical trials sponsored by the pharmaceutical industry.

Almost immediately, CEDPAP's activities started to be questioned. Complaints were heard from physicians in neighborhood health centers, which served a very low income population and were within the catchment area of the Children's Hospital. In response to criticisms raised by people with some knowledge of the situation, several agencies and organizations, including the Social Services area of the Catholic Church, the Medical Council of the Province of Cordoba and the Public Ombudsman, requested the municipal authorities to investigate (2006).

The Trade Union of Workers and Municipal Employees opposed the permission to meddle in the affairs of the municipal health facilities granted by the Agreement to CEDPAP, a private company, for the benefit of the pharmaceutical industry. This was the final straw, and the Cooperation Agreement between the Municipality and CEDPAP was annulled a few days after it had been signed (Franco 2006).

With the election of a new municipal government, the Municipality of Cordoba began an investigation of the Children's Hospital at the end of 2003, suspending all clinical research in the municipality. The Department of Human Rights in the Ministry of Justice and Human Rights asked Dr. Pedro Sarasqueta, Chief of the Neonatology Service in the Garraham Hospital, Buenos Aires, to prepare an Expert Report,[1] including an analysis of all the documents and complaints collected on the

[1] The requested Expert Report is an activity prior to an Administrative Inquiry.

situation at the Children's Hospital. Dr. Sarasqueta said in conclusions of his Report (Sarasqueta 2004):

1. The hospital had not estimated the cost of the supplies used, and did not compare the cost incurred with the benefits obtained from the clinical trials. Statements by hospital personnel indicated that (Sarasqueta 2004:1):

   > . . .in some current research, such as the pneumococcus surveillance study, increasing amounts of laboratory and radiological supplies are being used and paid for by the Children's Hospital of Cordoba, substantially adding to the operating cost of the hospital in these budget lines. Other testimony that will need to be evaluated during the Administrative Inquiry describes situations where essential blood cultures were not done for patients outside the study protocol due to lack of funds in the hospital budget, while those in the study received them because the supplies were provided by the sponsor

2. There was political interference because the study "Hospital-based surveillance to estimate the disease burden of rotavirus gastroenteritis in children less than three years of age in Cordoba, Argentina" was approved by the Minister of Health more than one month before receiving the scientific and ethical approval of the corresponding committees. And the IREC, which finally approved the study, carried the logos of the two institutions, reflecting the confusion between the Hospital and CEDPAP (Sarasqueta 2004:17)
3. The ethics committee of the hospital that approved the protocol of the anti-pneumococcal vaccine did not comply with existing regulations. The approval document included the name of CEDPAP and the name of the hospital, as well as the names of the principal investigator and co-investigator, who due to conflicts of interests should not be present during the discussion much less vote for the approval of the protocol.
4. The work of the hospital was impacted. As in many municipal hospitals operating with scarce resources, the presence of a number of clinicians who were not part of the hospital staff could (Sarasqueta 2004:22):

   > . . .produce a strong institutional imbalance between research and staff physicians with different tasks and very different remunerations, which can result in significant adverse changes in the implementation of the most important functions of public institutions, which is the provision of health care for predominantly low-income populations, whose only health resource are the public hospitals

   This is to say, there was differential access to necessary diagnostic tests and treatments: if the patient was a clinical trial participant he/she had preferential access while regular patients did not. There were instances when a clinical trial took place without the knowledge of the hospital staff, implying potential risks for the patient.

   Dr Sarasqueta acknowledged that this problem was due in part to the former Municipal Secretary of Health, who allowed a private institution to operate within public health facilities without controls, and without informing ". . .senior administrators, such as the Director General for Coordination of Primary Care" (Sarasqueta 2004:23).
5. According to information presented in the dossier, the consent to participate in the clinical trial was not always informed. One mother did not understand that

her daughter could be in the control group, and might not receive the vaccine. According to her testimony, she (Sarasqueta 2004:24):

> . . .was read only part of the informed consent, which was colored in yellow. She signed the document, then they gave her another part of the document which was white, with several sheets of paper, which she was not able to read before signing the consent

When she asked why her daughter had become ill during the study, she was told that her daughter had received the placebo, a word she did not understand and had to look up in a dictionary.

6. It was not ethical for CEDPAP to pay residents working in a clinical trial, since this was ". . .a distortion during a time of learning about professional standards" (Sarasqueta 2004 :35). Nor was it considered acceptable to pressure professionals working in municipal facilities to become involved in the clinical trials by collecting information, providing services to clinical trial participants, or recruiting patients. When municipal employees opposed these practices, the Municipal Secretary of Health replied (Sarasqueta 2004:35):

> It is the decision of this Secretariat that the issue be resolved and timely notification given to continue the studies with the possibility of imposing sanctions against those professionals employed [by this Secretariat] who do not comply with the directive

The evaluation report confirmed that the Municipal Secretary of Health had ceded power to the private sector for managing research, conducting interventions and providing care in municipal pediatric facilities.

After the Expert Report was received, the Municipal Government began an Administrative Inquiry in 2004 (Municipalidad de Córdoba 2005a). Following interviews with many people, the 364 page document resulting from the investigation confirmed the conclusions of the Expert Report, stating that:

- Municipal employees had been pressured to contribute to the implementation of clinical trials by recruiting patients under three years of age, drawing blood for tests, giving vaccinations, and performing other activities
- Informed consents were signed without properly informing parents or witnesses about the study protocol – including that blood samples were to be sent to another country – or explaining the risks assumed by participating in an experimental vaccine trial
- The protocol had been approved by an Ethics Committee which included the researchers
- Physicians, biochemists, radiologists, laboratory technicians, and nurses had been pressured, through monetary compensation or by management, to recruit the number of participants required by the protocol
- To comply with the study protocol, CEDPAP personnel worked in the Hospital and in clinics within its catchment area; they unlawfully gained access to medical records and classified documents, and made illegible notes that the hospital staff, who cared for patients prior to their enrollment in the trials could not understand; and

- CEDPAP physicians did not know how to treat adverse effects or they had been forbidden to do so

The document also stated that equipment donated to the hospital had disappeared, a situation that was reported to the Anti-Corruption Prosecutor.

Based on these and other charges, which are detailed in the document, and for reasons of space, are omitted, 12 municipal employees were disciplined for non-compliance with municipal ordinances. Of these 12, four were dismissed and eight suspended for 15 or 30 days (Municipalidad de Córdoba 2005b). The Chief of Pediatrics escaped sanctions as he reached retirement age and chose to retire.

One of the dismissed employees appealed the dismissal and received a majority decision for reinstatement. In addition, the municipality had to pay lost wages and a US$3,700 compensation for unjust dismissal (Cámara Contencioso Administrativo de Primera Nominación 2009). The trial judges did not discuss the possible ethical violations committed in the clinical trials, but explained why the employee should be reinstated. In their opinion, the administrative sanction was excessive. They questioned the reasons for not applying the same sanction to everyone involved in the clinical trials, and said that pressure from senior hospital personnel had caused the employee's actions.

The remaining cases were also acquitted (La Mañana de Córdoba 2009), and the Mayor, in his new electoral campaign, publically apologized to the Chief of Pediatrics, perhaps in response to the Chief's lawsuits against the Mayor, the Deputy Mayor, the Municipal Secretary and Sub-Secretary of Health, the Municipal Director of Medical Care, the ex-Director of the Hospital, and other physicians and union members. The grounds for the lawsuits were that when the municipal authorities discontinued the epidemiological surveillance in the region, they violated Article 205 of the Penal Code, which stated that it was an offense (Franco 2005):

> . . .to contravene the measures adopted by appropriate authorities to prevent the introduction or propagation of an epidemic.

In the Complaint filed by the Chief of Pediatrics, there were few references to the clinical trials and the alleged ethical violations, which were the foundation of the preliminary investigation (Franco 2005).

According to the Chief of Pediatrics, infant mortality had increased in the Municipality of Cordoba because the new administration had prevented the continuation of the epidemiological surveillance approved by previous authorities, which CEDPAP had been conducting without using public funds. There was no mention that the epidemiological surveillance was funded by a pharmaceutical company (in this case, by GSK, which was presumably financing this study to gather information for the development of vaccines). The Complaint stated that the Administrative Inquiry was a conspiracy against the Chief of Pediatrics (Franco 2005):

> At no time was there any intent to 'investigate' anything, only to find something to legitimize what had been previously decided: to eliminate Dr. Tregnaghi, his team, and all the scientific projects they were conducting

The Complaint added that the personal attack was a political decision, evidenced by the appointment of a Chief Investigator who "had a well-recognized feud" against him (Mac Lean and Degiorgis 2005).

The Chief of Pediatrics was charged with theft, but due to the statute of limitations (two years) the charge was dismissed. In his Complaint, he stated that he had reported the theft of equipment donated by GSK at his request, to the administration of the Children's Hospital.

Two former Chiefs of Residents in the Children's Hospital (2001–2002 and 2004–2005) made statements about the 'scientific nature' of the clinical trials. According to them, the function of the Argentine researchers was limited to collecting data and caring for patients (Mac Lean and Degiorgis 2005). And they noted that in Cordoba (Mac Lean and Degiorgis 2005:1):

> . . . after many years of scientific work in the Hospital, we should find a reliable practice of research or a scientific culture, which isn't there

They concluded that it could not be said that in Cordoba there was a clinical scientific community, but that there was a commercial activity of clinical trials in public hospitals that was used for private gain. One of the commercial products was a vaccine marketed by a foreign company and sold at a price outside the reach of the impoverished clinical trial participants.

> . . . Monetary payment was the principal stimulus for the hospital residents, noting that most did not receive a salary. . . [but] were even coerced by the Chief of Pediatrics. . . For years, the Chief of Pediatrics and head of CEDPAP paid US$20 to the resident on duty who found pneumonia on an X-ray, and the payment increased to US$50 if pneumococcus was found in the blood culture, and we do not think that this is the way to make science (Mac Lean and Degiorgis 2005:1)

5.3 Two Case Studies: COMPAS and the Hepatitis Vaccine Trials

5.3.1 The COMPAS Trial

Upon retirement, the Chief of Pediatrics ceased to work for the municipality, and since the Mayor had suspended his research, he could no longer use the Municipal Children's Hospital for his clinical trials. The clinical trials continued, however, because the Provincial Minister of Health welcomed the retired Chief, offered him the use of the Provincial Maternal-Neonatal Hospital and other provincial facilities, and made arrangements for his research to continue in other municipalities of the Province. In addition, in 2003, the Provincial Minister made the regulatory changes to Resolution 729, previously discussed.

The retired Chief of Pediatrics looked for other municipalities in Cordoba and in other provinces (see Chap. 4) to carry out the clinical trial of a GSK vaccine to prevent pneumococcal infections – known as the COMPAS trial. The COMPAS

trial was an international, multicenter trial that in the Latin American region included Panama, Colombia and Argentina, where they expected to enroll 24,000 children under one year of age. Argentina had the highest quota of 17,000 children, but recruitment was halted at 13,981.

With the support of the Provincial Ministry of Health, the city of Rio Cuarto in the municipality of the same name was chosen for the trial. Rio Cuarto has a population of 166,000 (2010) and is a service town for the rural communities of the municipality. At the beginning, only a few municipal clinics participated in the trial, but in 2005, all municipal clinics recruited children for the trial and a total of 331 babies were enrolled (Puntual 2005).

The Provincial Deputy Minister of Health said that the mothers of the children had received a detailed explanation of the nature of the clinical trial, and had to consent before their children could participate. He added that the vaccine had no risks for the children, that it was safe, and that all physicians of the municipality would be trained as "assistant researchers". Since the clinical trial was taking place in municipal facilities, and municipal personnel would be assistant researchers, it is probable that the municipality incurred some expenses; however, the amounts, spent, and the compensation offered by GSK are unknown. As explained in Chap. 4, the informed consent was poorly understood by mothers, and a few children enrolled in the trial in other provinces, died.

The Deputy Minister said (Orchuela 2006):

> Recently, in compliance with the protocol, we have been congratulated for the timely enrolment of more than 300 children

which unveils the interest of the provincial authorities in satisfying the speedy recruitment that multinationals demand from clinical trial researchers.[2] In 2009, as mentioned in Chap. 4, the principal investigator and GSK were fined by ANMAT for not complying with clinical trial guidelines during the implementation of COMPAS.

5.3.2 Phase II Study of the Immunogenicity of a Vaccine

According to clinicaltrials.gov, the purpose of the Sanofi-Aventis sponsored Phase II study comparing the immunogenicity of the combined DTaP-IPV-HB-PRP-T vaccine with Pentaxim and Engerix-B Pediatric vaccines in healthy Argentine children at 2, 4, & 6 months of age was "to demonstrate that the immune response in the month of receiving the three doses of the hexavalent vaccine (DTaP-IPV-HB-PRP-T) is not inferior to that generated after receiving the corresponding doses of

[2] For more information on how pharmaceutical companies value speedy recruitment see the Peruvian case study discussed in Chap. 12.

the association of Pentaxim and Engerix-B Pediatric." The secondary objective of this clinical trial was to describe the safety profile of the vaccines in the two groups.

The study was conducted by CEDPAP and the physicians of the Provincial Maternal Neonatal Hospital in Cordoba, with the approval of ANMAT and the Ministry of Health of the Province of Cordoba.

According to clinicaltrials.gov, the enrollment of 624 children in Cordoba began in October 2004 and ended in November 2005; despite the fact that the Council on Bioethics and Human Rights in Biomedical Research at the National Ministry of Justice announced in July, 2005, that (Tealdi 2005:13):

> . . . implementation should not be approved. If the study has started, it must be suspended with due care for the protection of research subjects

In Argentina, the National Ministry of Justice is obliged to investigate citizen complaints involving human rights violations and the number of petitions has increased in recent years.

The national Ministry of Justice issued a lengthy report, which included the following points: (1) the implementation of the study disrupted the national calendar for vaccinations, put children at risk, and, being a study aimed at changing public policy, it was approved without an analysis of its relevance and possible impact on the public health of the nation; (2) there were conflicts of interest in the ethics committee that approved the study; and (3) the study was approved by the ethics committee although it violated nine paragraphs of the Declaration of Helsinki and ten clauses of the Guidelines issued by the Council for International Organizations of Medical Sciences and the World Health Organization -CIOMS/WHO 2002.

The official immunizations calendar of Argentina requires the administration of the first dose of the Hepatitis B vaccine at birth, while the research protocol delayed the vaccine until two months of age in cases where the mother was not sero-positive for Hepatitis B. Delaying the administration of the vaccine would put Argentine children at risk for infection, which, at such a young age would considerably increase their possibility of developing chronic hepatitis, cirrhosis, and/or hepatic carcinoma later in life. For this reason, the World Health Organization made the recommendation (adopted by many countries) that the first dose of the vaccine be given at birth, especially where there are insufficient resources to analyze the presence of the hepatitis B antigen in pregnant women and trace the children of infected mothers. There are other criteria to be considered when evaluating studies aimed at altering public policy, as stated in this report (Tealdi 2005:9–10):

> Proof of Principle (POP) protocols, such as this, try to show to what extent a particular approach may work better than other immunization schedules. . . These studies do not have a direct and immediate benefit for the population under study. . . In these cases it is necessary to establish agreements between the sponsor and the regulatory authority and decide up to what point the proposed research may benefit the public health of the population and may be sustainable as public policy strategy. . . All studies in pediatric populations must be strictly regulated and controlled by the national authority, making it necessary to establish a national review system for biomedical research in general and for research on vaccines in the pediatric population in particular

As in other studies, the principal investigator was also the chairman of the ethics committee, which approved the study, and

> . . . in spite of this, neither the informed consent nor the body of the protocol identified the existence of possible conflicts of interest. . . Similarly there was not any mention regarding the budget of the study and eventual disbursements such as honoraria or other payments that the researchers may receive (Tealdi 2005:10)

In addition, the evaluation by the Ministry of Justice documented the following problems: (1) the informed consent form was incomplete and had erroneous information, (2) a vulnerable population was not adequately protected, and primacy was given to scientific interest instead of human wellbeing, (3) the protocol omitted important scientific information and did not provide a careful risk – benefit evaluation for the study, and (4) there was a difference in ethical standards for the sponsor country as compared with the guest country (Tealdi 2005:12).

Later, September 20, 2005, the European Medicines Agency withdrew the vaccine that had been used in the Argentinean experiment from the European market because of its low immunogenicity against Hepatitis B (EMEA 2005). However, clinicaltrials.gov shows that nine studies using that vaccine were taking place after that date using vulnerable populations – children living in medium- and low-income countries (see Table 5.1).

5.4 Discussion

This chapter shows the political dimensions of clinical trials. The changes to provincial regulations that took place in Cordoba did not result from clinical advances or new ethical approaches to clinical research, but from the interests of elected officials and their appointed staff. The first provincial regulation was based on internationally recognized ethical principles. It has been acknowledged that compliance with these principles may delay the conclusion of the clinical trials and increase their cost, and consequently, the sponsors and the principal investigators have an interest in introducing modifications to the regulations. Some elected officials were more vulnerable to the lobbying of the investigators than others.

CEDPAP was an influential institution. The Director of the Municipal Children's Hospital told all hospital staff that CEDPAP should be considered the research unit of the public hospital. That for the Provincial Ministry of Health, supporting vaccine clinical trials had become a provincial policy could be attributed to lobbying. One Minister of Health opened the doors of the Provincial Maternal Neonatal Hospital to the ex-Chief of Pediatrics of the Municipal Children's Hospital – who was not allowed to continue clinical trials in the municipality due to serious allegations of regulatory and ethical violations – to conduct clinical trials.

The political dimensions of defining clinical trial regulations are also illustrated by the reaction of private foundations to the regulation that disallowed IRECs in

Table 5.1 Studies of DTaP-IPV-HB-PRP-T sponsored by Sanofi-Aventis registered at Clinicaltrials.gov (January 25, 2011)

Identification number	Phase of study	Place	Participant characteristics	Sample	Participant registration period
NCT00831311	Phase II	Argentina	Healthy children, 2, 4 years 6 months	624	October 2004–November 2005
NCT00303316	Phase III	Argentina	Children between 510 and 578 days, who had participated in NCT00831311	459	February 2006–April 2007
NCT00313911	Phase III	Mexico, Peru	Healthy children, 2, 4 years 6 months	2,133	July 2006–January 2008
NCT00315055	Phase III	Turkey	Healthy children, 2, 4 years 6 months	310	July 2006–July 2007
NCT00362336	Phase III	South Africa	Healthy children, 6, 10, 14 weeks	622	August 2006–May 2008
NCT00401531	Phase III	Thailand	Healthy children, 2, 4 years 6 months	412	October 2006–November 2007
NCT00404651	Phase III	Mexico	Healthy children, 2, 4 years 6 months	1,189	November 2006–April 2008
NCT00619502	Phase III	Turkey	Healthy children, 15–18 months, who had participated in NCT00315055	254	December 2007–September 2008
NCT00654901	Phase III	Mexico	Healthy children, 456–578 days, who had participated in NCT00404651	881	March 2008–May 2009
NCT00831753	Phase III	Peru	Healthy children, 50–71 days of age	266	May 2008–May 2009

Source: Prepared by the authors from www.Clinicaltrials.gov
Hexavalent vaccine DTaP-IPV-HB-PRP-T
DTaP Diphtheria-Tetanus-acellular Pertussis Vaccines, *IPV* inactivated polio vaccine, *HB* hepatitis type B, *PRP-T* Each dose of lyophilised PRP-T vaccine is formulated to contain 10 mg of polyribosylribitol phosphate chemically conjugated to 24 mg of tetanus toxoid
http://clinicaltrials.gov/ct2/show/NCT01177722

institutions that did not offer medical care. Through lobbying, these private organizations were successful in reversing the regulation.

The lobbying power of clinical trial researchers should not be disregarded. As their relations with powerful transnational pharmaceutical corporations solidify, they acquire professional prestige. Thus, the Chief of Pediatrics of the Children's Municipal Hospital was a member of the permanent advisory council of the Latin American Society for Pediatric Infectious Diseases, and received a prize from the International Organization for Training and Medical Research (IOCIM) in recognition of his clinical research career.

This chapter also illustrates the behavior of the pharmaceutical industry. GSK did not appear to be concerned by the allegations raised by the municipality against the Chief of Pediatrics and maintained him as principal investigator of COMPAS, only to confirm several years later – through the courts – that national regulations had been violated during the implementation of the trial. We can suggest that when a pharmaceutical industry decides that a physician delivers, it will keep him/her as principal investigator for years to come. For the pharmaceutical industry, delivery means, among other things, successful lobbying and expeditious completion of trials. The fines imposed do not appear to be a deterrent to continue business as usual.

The Sanofi-Aventis clinical trial also shows the successful lobbying that private provincial institutions involved in clinical trials can have at the national level. CEDPAP continued the trial even after the European Medicine Agency had withdrawn the vaccine from its market. ANMAT and the Provincial Ministry of Health did not raise any concern, and the National Ministry of Justice seemed to be unable to stop the trial.

In Cordoba, most participants in clinical trials are poor and indigent, and are recruited primarily by their attending physician. At the end of the trial, if a medicine is commercialized, the participants will not be able to access it because of its high price. If the poor and indigent happen to be children, then we have a case of double vulnerability.

Finally, the concerns of the Municipality of Cordoba raise an additional important question. The staff of the hospitals and clinics was concerned about the interference and health risks caused by the physicians and other health workers contracted for the clinical trials. The municipal health workers considered unethical the fact that clinical trial participants were treated differently than ordinary patients, that is to say that the former received better care than the latter.

References

Ávila Vázquez, M. 2007. Globalización e identidades médicas en los ensayos clínicos. (Globalization and medical identities in clinical trials) *Salud Colectiva* 3(3): 235–245.

Barlett, D.L., and J.B. Steele. 2011. Deadly medicine. *Vanity Fair*, January. http://www.vanityfair.com/politics/features/2011/01/deadly-medicine-201101?printable=true&currentPage=all. Accessed 27 Oct 2012.

Boletín Oficial. Provincia de Córdoba. 2007. Crean el sistema de evaluación, registro y fiscalización de los investigadores en salud (A system to evaluate, register and supervise clinical researchers is created). Boletín Oficial. Provincia de Córdoba. Resolución no. 2. Tomo 17 (Resolution number 2, volumen number 17), Jan 24.

Cámara Contencioso Administrativo de Primera Nominación. 2009. Sentencia Judicial a favor de empleada municipal que fue separada de su trabajo por colaboración con el Dr. Tregnaghi (Court Decision in favor of municipal employee who was dismissed due to having collaborated with Dr. Tregnaghi).

EMEA. 2005. Press release. European Medicines Agency recommends suspension of Hexavac. EMEA/297369/2005. http://www.medicinesauthority.gov.mt/pub/29736905en.pdf. Accessed 28 Oct 2012.

Fernández, M. 2005a. Córdoba: Laboratorio médico de Argentina (Cordoba: Medical Laboratory of Argentina). La Voz del Interior (Córdoba), 2 Oct. http://archivo.lavoz.com.ar/2005/1002/sociedad/nota361306_1.htm. Accessed 27 Oct 2012.

Fernández, M. 2005b. Argentina, Córdoba: Más personas controlarán ensayos clínicos (Argentina, Cordoba: More people will control clinical trials). La Voz del Interior (Córdoba), 17 Nov. http://archivo.lavoz.com.ar/2005/1117/UM/nota372128_1.htm. Accessed 27 Oct. 2007.

Fernández, M. 2006. Salud frena nuevas investigaciones médicas (Health ministry delays new medical research). La Voz del Interior (Cordoba), Dec 4. http://archivo.lavoz.com.ar/nota.asp?nota_id=24090. Accessed 27 Oct 2012.

Franco, G. 2005. Denuncia formulada por el Dr. Miguel Tregnaghi al Sr. Fiscal de Instrucción (Complaint from Dr. Miguel Tregnaghi to the Prosecutor during the Preliminary Inquiry).

Franco, G. 2006. Letter from the lawyer of Dr. Miguel Tregnaghi to Dr. Nuria Homedes.

Gobierno de Córdoba. Ministerio de Salud. 2007. Resolución 1618 Art. 17 bis (Resolution 1618, Art 17 bis), 28 Dec. http://www.cba.gov.ar/wp-content/4p96humuzp/2012/07/sal_coeis_resol1618.pdf. Accessed 28 Oct 2012.

La Mañana de Córdoba. 2009. Fallo judicial a favor de médicos echados por juez (Court Decision in favor of physicians dismissed by the judge), 13 May. http://www.treslineas.com.ar/fallo-judicial-favor-medicos-echados-juez-n-93373.html. Accessed 28 Oct 2012.

Mac Lean, B., and D. Degiorgis. 2005. Investigaciones científicas privadas en el hospital infantil (Private scientific research in pediatric hospital). La Fogata, Sept. http://www.lafogata.org/05arg/arg10/arg_26-13.htm. Accessed 2 Nov 2012.

Ministerio de Salud. 2006. Situación de la ética de la investigación biomédica en la Provincia de Córdoba (Assessment of the ethical situation of biomedical research in the Province of Cordoba). Ministerio de Salud. Ministerio de Salud, Provincia de Córdoba, Área de Bioética, Cordoba.

Municipalidad de Córdoba. 2005. Proyecto de Decreto. Documento no. 3675 (Draft of decree. Document number 3675), 30 Aug. http://www.cordoba.gov.ar/cordobaciudad/principal2/docs/democracia/salud/Proyecto_de_Decreto_Expte_942681_03__Htal_Infantil.pdf. Accessed 28 Oct 2012.

Municipalidad de Córdoba. 2006. Participación Ciudadana. Caso Hospital Infantil. Sumario Administrativo Municipality of Cordoba (Citizenry participation. Case of the Pediatric Hospital. Preliminary evaluation), 27 Sept. http://www.cordoba.gov.ar/cordobaciudad/principal2/default.asp?ir=42_4. Accessed 28 Oct 2012.

Municipalidad de Córdoba. 2007. Presentación al Informe de Peritaje del Dr. Sarasqueta (Introduction to the expert report by Dr. Sarasqueta). Córdoba. Municipalidad de Córdoba.

Municipalidad de Córdoba. Dirección de Sumarios e Investigaciones. 2005a. Reporte final no 03/05 Expediente No 942.681/03 (Final Report number 03/05 Ref: Expte. No 942.681/03), 23 Aug. http://www.cordoba.gov.ar/cordobaciudad/principal2/docs/democracia/salud/Proyecto_informe_final_Htal_Infantil_mail_elina%202.pdf. Accessed 28 Oct 2012.

Orchuela. J. 2006. Investigaciones clínicas con medicamentos y vacunas en hospitales públicos de Córdoba y Santiago del Estero fuertemente cuestionadas (Clinical research with drugs and vaccines in the public hospitals of Cordoba and Santiago del Estero have been strongly questioned). *Boletín Fármacos* 9(1): 100–105.

Puntual. 2005. El laboratorio Glaxo prueba una vacuna con 330 bebés riocuartenses (Glaxo test a vaccine on 330 babies at Rio Cuarto), 8 Nov.

Sarasqueta, P. 2004. Informe de peritaje: Caso Hospital Infantil Municipal de la ciudad de Córdoba (Evaluation report: Pediatric Municipal Hospital of Cordoba). Municipalidad de Córdoba.

Tealdi, J.C. 2005. Solicitud de opinión sobre ensayo clínico: Estudio fase II de inmunogenicidad de una vacuna combinada DTaP-IPV-HB-PRP-T comparada con PENTAXIM y ENGERIX B

Pediátrico a los 2, 4, y 6 meses de edad en niños argentinos sanos. Consejo de Ética y Derechos Humanos para las Investigación Biomédicas. Secretaría de Derechos Humanos- Ministerio de Justicia y Derechos Humanos Coordinator (Request of opinion about the clinical trial: Phase II Immunogenicity of DTaP-IPV-HB-PRP~T Combined Vaccine Compared With PENTAXIM™ and ENGERIX B® at 2-3-4 Months Schedule in healthy Argentinean children. Ethics and Human Rights Council for biomedical research. Human Rights Secretariat- Ministry of Justice and Human Rights Coordinador). Buenos Aires, 8 July.

Vidal, S. 2006. Ética o mercado, una decisión urgente. Lineamientos para el diseño de normas éticas en investigación biomédica en América Latina (Ethics or market, an urgent decisión. Guidelines for designing ethical norms for biomedical research in Latin America). In *Investigación en seres humanos y políticas de salud pública* (Research with humans and public health policies), ed. M.G. Keyeux, V. Penchaszadeh, and A. Saada, 191–232. Bogota: Unibiblos and Redbioética UNESCO.

Chapter 6
Brazil: The System for the Protection of Voluntary Participants in Research

Corina Bontempo Duca de Freitas, William Saad Hossne, and Susie Dutra

6.1 First Steps in Research Involving Humans

Discussions on the establishment of ethical parameters and the regulation of clinical trials with human participants began in Europe and the United States in the 1950s, gaining increasing emphasis during the 1970s and 1980s. In Brazil, clinical research grew during the 1980s, when investigators from Europe and the USA invited major Brazilian centers – public hospitals and academic centers – to take part in clinical trials. As a result, the first centers for research were established, and, as in other parts of the world, some incidents happened which caused concern and illustrated the need for regulations to protect study subjects. The Norplant study was a major case in point.

Norplant, a long-term (five years) contraceptive, developed by the Population Council of the United States, consists of six capsules of levonorgestrel inserted beneath the skin (Israel and Dacach 1993). Norplant began to be used in Brazil in the mid-1970s, but was not reviewed by the health authorities until 1984. At that time the country had a military government, many universities had links with population centers, and ethical standards were lowered. For example, when the University of Campinas presented the Norplant project to the health authorities in 1984, the President of the University was a member of the advisory committee of the Population Council, and the study was approved without fulfilling fundamental ethical standards. The study did not require women to give informed consent, the

C.B.D. de Freitas (✉)
Coordenação de Pesquisa e Comunicação Científica, Fundação de Ensino e Pesquisa em Ciências da Saúde – FEPECS, Brasilia, Brazil
e-mail: corinabdf@gmail.com

W.S. Hossne
BIOÉTICA, Centro Universitario São Camilo, São Paulo, Brazil

S. Dutra
Comitê de Ética em Pesquisa, Fundação Hemominas, Belo Horizonte, Brazil

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_6,

use of the product was illegally promoted in the mass media, the number of recruitment centers grew from seven to 21 without previous authorization, and the number of women recruited in the study was also greater than the approved sample. Between August 1984 and January 1986, 3,562 mostly poor women were recruited into the study when permission had been given for only 2,000 study participants. Additionally, although it had been presented to the health authorities as a Phase III study, the 1984 annual report of the Population Council stated that it was a clinical trial to promote Norplant (Dos Reis 1990).

With the return of a democratic government, feminists demanded a review of birth control programs in Brazil, which led to the formation of a Commission for the Study of Women's Reproductive Rights in the Ministry of Health. Following the review of two Norplant studies, one in Rio de Janeiro (Koifman report) and the other in Campinas – Fortaleza and Curitiba (Hardy report), which documented the occurrence of the ethical abuses mentioned above and the emergence of adverse events that remained unattended, the authorization to conduct clinical trials with Norplant was cancelled on January 22, 1986.

The 1988 reform of the Brazilian Constitution strengthened the National Health Council (Conselho Nacional de Saúde – CNS), composed of representatives of users, agencies, and health care workers, with the objective of increasing social control and community participation in health sector management. These events had international repercussions (Vieira and Hossne 1987), the CNS prioritized the regulation of research involving humans and in 1988 approved Resolution Number 1. This resolution included the first standards for health research and discussed the need to form research ethics committees. For its part, the agency responsible for health surveillance and for authorizing the importation of medications for clinical trials released its Manual of Procedures, which included a Risk Recognition Form, as a way of self-protection against possible accusations from study participants (or their families) who felt they had been harmed by participating in clinical trials of products not approved for use in humans.

As Brazilian researchers were included in international trials, the CNS, especially its Committee on Science and Technology (CICT), was confronted with ethical questions, which had not been foreseen in the first resolution. For example, the military had conducted secret experiments, there were internationally supported studies that had not been approved in the country of origin, and studies had taken place in accredited Centers of Excellence where the level of risk to participants was so high that it was said that study subjects had become human guinea pigs. There is evidence that healthy soldiers were exposed to Leishmaniasis to test the effectiveness of a new treatment; also, contrary to Brazilian therapeutic guidelines, AIDS patients included in the control group of one clinical trial were denied triple antiretroviral treatment.

Seven years after the first Resolution, a study confirmed the need to modify and strengthen the protections for human research participants. Few ethics committees had been formed, the scientific community did not recognize the ethical standards, and society in general was totally uninformed. There had

been important problems in the implementation of the regulation; for example, there were no strategies to form ethics committees or training programs to help them understand and execute their functions (Francisconi et al 1995). The responsibilities of the researchers and those of the CICT were not clearly separated; for example, the system allowed accredited centers that had been supervised during the implementation of a clinical trial to conduct, during a specified period, other research projects – regardless of their design and complexity- without notifying the CICT.

6.2 Engaging Communities in the First Revision of the Regulations

The premises governing this revision of the regulations were as follows:

1. The regulations will apply to all establishments and investigators conducting research involving human beings, no matter in which area of knowledge gains are sought, and they will not be limited to the research conducted in health centers and hospitals. This important change was based on the premises that the amount of science and technology research would increase, and that any project involving human subjects holds risks and uncertainties which cannot always be foreseen or prevented, but which may affect the health of study participants (Hossne 2003). At that time, health was considered not to be merely the absence of disease, but the balance between individuals and their environments, and it involved aspects of physical, psychological, and social wellbeing
2. The regulations will be based on updated ethical principles
3. The final product will reflect Brazilian culture and ideas, which will be unveiled through consultations and meetings for community input

This was the first time that Brazilian decision-makers sought the involvement of communities and experts, and engaged in a wide consultation process. The first step was to identify the organizations and people to get involved. It was decided to include, among others, researchers and administrators of facilities conducting research with human subjects, experts in the analysis of bioethics in public policy, scientific associations, universities, research centers, professional associations, human-rights groups, experts in health law, consumer advocacy groups, women's movements, disease-oriented associations (i.e., diabetes association, AIDS-patients groups, etc.), and religious institutions. In addition, other experts were invited to guide the group in addressing ethical dilemmas, such as research involving human reproduction, genetics, bio-security, indigenous populations, new medications and vaccines, and new devices and equipment for the diagnosis and treatment of health problems.

Understanding the social repercussions and the multidisciplinary nature of protecting human research participants, the CNS delegated responsibility for updating the existing regulations to a multidisciplinary working group with representatives from all interest groups.[1]

The members of the coordinating group were responsible for engaging other members of their agencies and organizations in the discussion and in the various scientific events that were organized around the general theme of bioethics in clinical research. Box 6.1 lists the principal strategies used in this process. After a thorough review of international codes and national regulations, a first draft of the new regulatory framework was produced and 2,300 copies were mailed along with letters soliciting comments and suggestions to incorporate in the new regulation.

To encourage participation and to include the opinions of other groups, information about the project was published in the National Medical Council's journal, Bioética (CFM), as well as in 20,000 copies of the National Health Service epidemiological newsletter. The Tenth National Conference on Health included a session on this subject, and other scientific organizations, professional and non-professional associations, and universities held seminars to facilitate the interchange of ideas. Several institutions established work groups and submitted documents explaining their position and suggestions, and the press and other media produced articles and reported on the progress and challenges of this great social movement.

[1] Participants included the National Medical Council (Conselho Federal de Medicina – CFM), the National Feminist Network for Reproductive Health and Rights (Rede Nacional Feminista de Saúde e Direitos Reprodutivos – REDE), the Brazilian Bar Association (Ordem dos Advogados do Brasil – OAB), the Brazilian Bishops Conference (Conselho Nacional dos Bispos do Brasil – CNBB), the Society of Theology and Religious Sciences (Sociedade de Teologia e Ciências da Religião – SOTER), the Brazilian Association of Medical and Dental Device Manufacturers (Associação Brasileira da Indústria de Equipamentos Médico- Odontológicos – ABIMO), the Brazilian Society of Biomedical Engineering (Sociedade Brasileira de Engenharia Biomédica – SBEB), the pharmaceutical section of the National Confederation of Industry (Confederação Nacional da Indústria – CNI), the National Research Institute, Ministry of Science and Technology (Conselho Nacional de Desenvolvimento Científico e Tecnológico do Ministério de Ciência e Tecnologia – CNPqMCT), the Department of Coordination of Scientific and Technology Development of the Ministry of Health (Coordenação de Desenvolvimento Cientifico e Tecnológico do Ministério da Saúde – DECITMS), the National System of Sanitary Surveillance, Ministry of Health (Secretaria de Vigilância Sanitária, Ministério da Saúde – SNVS), consumer representatives of the Brazilian National Health System (Usuarios del Sistema Único de Salud – SUS), representatives of disease-specific non-governmental organizations (ONGs), and researchers from Fiocruz (Oswaldo Cruz Foundation) – the research agency based in the Ministry of Health.

Box 6.1: Method Used to Develop Regulations to Incorporate Ethics Principles in Research Involving Human Subjects

- Frequent discussions with the scientific community and the general population about the existing guidelines, and inviting suggestions for their improvement
- Circulation of the current international guidelines for biomedical research
- Incentives for institutional seminars for in-depth discussions on the subject
- Seminars for representatives of non-profit organizations with interest in specific diseases, and other groups of clients of the national health system
- Consolidation of the proposals and suggestions
- Presentation of a draft document of the new regulations in a public meeting
- Presentation of the draft proposals for the new standards at the Brazilian Congress of Bioethics
- Presentation and approval of the final version of the regulations at the CNS and the 10th National Health Conference

After analyzing all the documents, reports, suggestions offered in writing and during community meetings and scientific events, the Coordinating Group produced a draft document and invited the comments and suggestions from experts and organizations. This document was also presented in a public meeting, where various interest groups and national agencies had the opportunity to critique it and share their thoughts and ideas.

It should be acknowledged that the HIV/AIDS organizations played an important role during this whole process. They were well organized, and challenged the authorities for granting permission for a study involving Indinavir that violated basic ethical principles. In this study, some participants could only use one medication, and they did not have access to the results of their blood tests, which are necessary to monitor the treatment and evaluate the course of the disease. Eventually, the National Commission terminated this study in Brazil.

In this manner, through cooperation between the general population and the government, a new set of regulations were developed and organized community groups would be responsible for overseeing scientific research. In other words, scientific research was placed under social control. Society in general would ensure adherence to resolution CNS 196/96 entitled Guidelines and Norms Regulating Research Involving Human Subjects (Diretrizes e Normas Regulamentadoras de Pesquisas Envolvendo Seres Humanos) (Ministerio de

Saude 2006),[2] which is still in effect. In the case of clinical trials with especially regulated products, a system of coordination would be established with the National Agency of Sanitary Surveillance (ANVISA), established on January 26, 1999 through Law 9.782.

6.3 Resolution CNS 196, 1996: Guidelines and Norms Regulating Research Involving Human Subjects, and Supplementary Standards

Resolution CNS 196/96 established the ethical requirements and scientific fundamentals to guarantee the rights of human subjects taking part in clinical studies. It recognized that any research with humans carries risks, physical or psychological, individual or collective, making it necessary to design control mechanisms to preserve the health (physical, mental, or social) of those involved. According to the resolution, any study involving human subjects must be approved by an institutional Committee for Research Ethics (in Portuguese, Comitê de Ética em Pesquisa – CEP), composed of members without any conflict of interest with the researcher or the sponsor; and while the principal investigator bears the primary responsibility for respecting the ethical principles and submitting the protocol for review, the ethics committee is also responsible for ensuring that the study is conducted in an ethical manner.

This Resolution also created the National Commission for Research Ethics (Comissão Nacional de Ética em Pesquisa – CONEP), which is the national entity responsible for coordinating and supervising the entire system. CONEP is accountable for enforcing the norms and resolutions of the National Health Council (CNS) and has regulatory, advisory, and training functions. Several study types – including multi-center clinical trials – require CONEP to analyze the research protocols approved by a CEP. CONEP can either ratify or question the CEP's decision and when the disagreements are not resolved, CONEP's opinion is binding for all research centers in the country involved in the study. The composition of the CEPs and CONEP is multidisciplinary, and includes experts on research, bioethics, law, health, social sciences, community representatives, as well as clients of the institution where the research takes place.

The CNS 196/96 Resolution has nine chapters (Conselho Nacional de Saude 2000). The first chapter, the Preamble or Introduction, discusses the regulations in the context of constitutional and civil law; the second chapter gives definitions; the

[2] Members of the executive group responsible for Resolution 196/66: William Saad Hossne (Coordinator), Sérgio Ibiapina Ferreira Costa, Artur Custódio Moreira de Souza, Fátima Oliveira, Leocir Pessini, Simone Nogueira, Jorge Bermudez, Márcio Fabri dos Anjos, Marília Bernardes Marques, Álvaro Antonio da Silva Ferreira, Antonio Fernando Infantosi, Albanita Viana de Oliveira, Omilton Viscondi; Executive Secretary: Corina Bontempo de Freitas.

third describes ethical issues in research involving humans; the fourth discusses the characteristics of freely given and informed consent; and the fifth discusses the benefits and risks of study participation. Chapters 6, 7, 8, and 9 refer to setting up and conducting the study, including the flow diagram for project approval and the distribution of responsibilities among the different participants and institutions.

The ethical guidelines emphasize compliance with the fundamental standards listed in Box 6.2, which are based on universally accepted bioethical principles (Hossne 2006). Bioethics is rooted in classical ethics together with the more recent theories of Kant, and of human rights, described by Beauchamp and Childress (2008). Included also, are ethics of responsibility, of caring, of the plurality of moral perspectives, and Latin American values of solidarity, equity, and collective health.

Box 6.2: Ethical Standards for Research Involving Human Subjects

- The study should be of sufficient scientific quality and should be based on any previous animal or laboratory studies
- Benefits must exceed risks for the participant
- If it is necessary to use a placebo, the principle of "do no harm" must be respected
- Participants in the study must give their free and informed consent, as explained in Chapter IV (CNS 196/96) "Termo de Consentimento Livre e Esclarecido" (Freely Given and Informed Consent)
- There must be a system to assure privacy and confidentiality of information
- The study will preferably recruit autonomous individuals as study subjects. If vulnerable or disadvantaged persons are included, there must be specific mechanisms for their protection
- The study must respect social and cultural values
- If the participants have benefited from the treatment, they must have guaranteed access to the study products or therapy after the study is completed
- The study must benefit the participants and their communities
- There must not be any conflict of interest
- International studies must include Brazilian researchers and institutions, there must be an advantage to participants and the nation, and the study must have been initially approved in the country of origin
- Biological material and information obtained may only be used for the approved study
- Full attention must be guaranteed to participants; compensation may not be withheld in case of possible harm, and the only indications for dismissing a study subject would be for reasons of security or protection from greater risk
- Voluntary participants may not receive financial remuneration, but their study-related expenses (e.g. for transportation or meals) may be covered

CNS 196/96 was later expanded in response to experience gained from the most frequent ethical dilemmas, which generated discussion among those involved in bioethics and clinical research, and the reports of studies in different scientific areas (see Table 6.1). The National Health Council, through CONEP, passed Resolution 251/97 to address issues involving research for new medications, and Resolution 292/99, which relates to international projects. The latter (292/99) established that studies with international cooperation must include Brazilians as partners with shared responsibility for the implementation of the project; that no international project could take place without prior approval, and without the recruitment of participants in the country of origin; and if these conditions are not relevant to a study, the researchers must inform the Ethics Committee (CEP), which will evaluate if the benefits and risks are equitably distributed among the parties involved.

These standards, developed in accordance with requests from the government, the scientific community, study participants, and society in general, reflect the wishes of the citizens and the promise to defend human rights. Their objective is to assure that studies comply with ethical principles, and that the interests and well-being of individual human subjects take precedence over those of society and of science.

6.4 Health Regulations for the National Health Surveillance Agency

The National Health Surveillance Agency (ANVISA) is responsible for monitoring studies of bioavailability and bioequivalence, which are mandatory for the registration of generic medicines and other new medications. Resolution RDC N°. 103/2003 requires these studies to take place in certified centers, and there is an inspection program to guarantee quality (see Table 6.1).

More recently, Regulation RDC 34/2008 was approved. This regulation created a register of study participants and an information system covering studies on pharmaceutical equivalence and bio-equivalence to prevent volunteers from simultaneously participating in several trials, being exposed to unnecessary risks, or potentially biasing the study results (for example, by too frequent participation or by enrolling in more than one bioequivalency study at the same time). These issues had been addressed in Resolution CNS 196/96, which required participants to wait 12 months before enrolling in another study and prohibited payment for participation or for daily wages lost due to participation in the study. It was considered that these payments could unduly attract people from the lower socio-economic classes. The regulation did allow payment of expenses for meals and transportation, but there was no mechanism to ensure compliance with these standards and it had been noted that a large number of study participants came from vulnerable situations, seizing the opportunity to take part in clinical trials while ignoring excess risk. This is an important ethical problem, which has been inadequately discussed by the scientific community.

Table 6.1 Principal regulations in Brazil for the conduct of clinical trials

Year	Regulation	Authority	Major content	Current status
1996	Law N°. 9279	National Congress	Regulates the rights and obligations in relation to the protection of intellectual property	In force
1996	Resolution N°. 196	CNS	Ethical principles and standards for the protection of human subjects in clinical trials	In force
1997	Resolution N°. 240	CNS	Defines the inclusion of user representatives in the Committees for Research Ethics (CEPs)	In force
1997	Resolution N°. 251	CNS	Regulates research with human subjects for new pharmaceuticals, medications, vaccines, and diagnostic tests	In force
1999	Law N°. 9782	National Congress	Restructures the National System of Sanitary Surveillance, and created ANVISA	In force
1999	Law N°. 9787	National Congress	Generic medications	In force
1999	Resolution N°. 292	CNS	Regulates research directed by foreign companies, or which takes place with foreign participation	In force
2000	Resolution N°. 303	CNS	Regulates human reproduction research	In force
2000	Resolution N°. 304	CNS	Regulates research involving indigenous populations	In force
2003	Resolution N°. 103	ANVISA	Certification of centers that conduct studies on bioequivalence and bioavailability	In force
2004	Resolution N°. 340	CNS	Regulates research in the area of human genetics	In force
2004	Resolution RDC N°. 219	ANVISA	Regulates the authorization for clinical trials with medications and health products (later included in the standards for health surveillance)	Revoked
2005	Resolution N°. 346	CNS	Regulates multicenter projects	In force
2005	Resolution N°. 347	CNS	Regulates the storage of samples taken from human subjects, and the use of biological samples obtained during previous studies	In force
2005	Law N°. 11.105	National Congress	Creates the National Biosafety Council (Conselho Nacional de Biossegurança – CNBS), and restructures the National Technical Committee on Biosafety (Comissão Técnica Nacional de Biossegurança) (CTNBio)	In force
2007	Resolution N°. 370	CNS	Regulates the registration and accreditation, and the renewal of registration and accreditation, of the CEP's	In force

(continued)

Table 6.1 (continued)

Year	Regulation	Authority	Major content	Current status
2008	Resolution RDC Nº. 39	ANVISA	Regulates the approval and monitoring of clinical research involving medications and health products, revoking RDC 219/2004	In force
2008	Resolution Nº. 404	CNS	Standards for placebo use, and access to medications when a study is completed	In force
2008	Resolution RDC Nº. 34	ANVISA	Instituted the information system for studies of bioequivalence and bioavailability	In force
2008	Resolution Nº. 1885	National Medical Council	Regulates the use of placebos in research conducted by physicians	In force
2009	Resolution Nº. 421	CNS	Increases CONEP members from 13 to 15, ensuring representation by CNS Directors (including employees, managers, and users of the Unified Health System)	In force

ANVISA developed procedures for the approval of clinical trials with new medications (Phases I to III) and to grant permits for the importation of the experimental drug. As part of this process, ANVISA requests CONEP to provide information demonstrating that the proposed study meets the ethical guidelines established by the CNS and analyses the study protocol and the characteristics of the sponsor and institutions where the study will take place. If ANVISA is satisfied after reviewing these documents, it will release a special communication allowing the study to proceed and granting permission for the importation of the new medication for the implementation of the clinical trials.

Regulation RDC Nº 39, 2008, is currently governing the approval process by ANVISA (2008). It states that ANVISA must be informed of all adverse effects arising during the clinical trial, allows ANVISA to conduct inspections of the research centers – with or without CONEP- and apply sanctions if infringements of Best Clinical Practices are found. ANVISA also regulates the Contract Research Organizations (CRO's), which, through contracts with the study sponsors, facilitate the implementation of clinical trials in Brazil and are often responsible for all communications between the sponsor, ANVISA and the principal investigator.

The 2008 Regulation speeds the approval process for clinical trials by permitting simultaneous (or parallel) evaluation by CEP-CONEP and ANVISA instead of the previous sequential system (see Fig. 6.1). In this manner, ANVISA may approve the importation of experimental medications when the first Committee for Research Ethics (CEP) approves a multi-center project, without waiting for CONEP's approval, but the sponsor may not begin a study until CONEP's approval has been received. An enforcement mechanism must be established to ensure that this condition is met.

6.5 The CEP-CONEP System

The ethical evaluation of research involving humans is performed through the CEP-CONEP structure, which is part of the National Health Council (CNS). The final approval of clinical trials of new pharmaceuticals and other health products, as mentioned earlier, also involve ANVISA. Until recently, the CEPs of all the establishments where the study was to be conducted and the CONEP had to approve a project before ANVISA could authorize it and issue an importation license for the experimental drug or device to be tested in the trial. As mentioned in the previous section, a relatively recent change allows ANVISA to proceed with its work simultaneously with the CEPs' review, with the restriction that the sponsor may not begin the project until CONEP's consent has been received (see Fig. 6.1).

Both the CEPs and CONEP are agencies of *munus publicum* (i.e. their mission is for the public good); they are multidisciplinary and inter-professional, and include representatives of the users of the system; they function independently from the sponsor and the investigator, and they defend the interest and rights of the study participants. Committee members are volunteers who receive no employment contract or remuneration for their work on these committees, and are selected based on criteria of availability and commitment to ethical standards and defense of human rights.

The CEPs are collegial bodies created by the institution they serve and although they receive logistical support they are independent of the management of the institution. All CEPs must be approved by CONEP, based on pre-established criteria, and, with the principal investigator, are co-responsible in assuring that the research

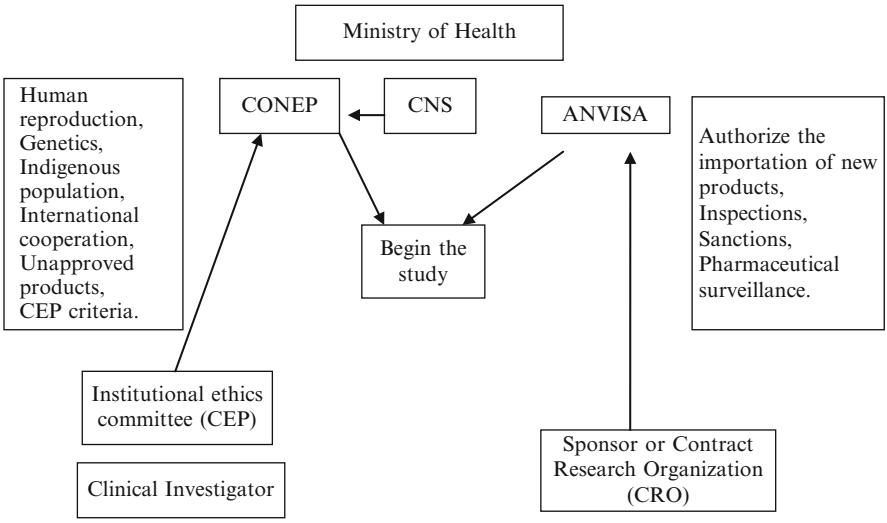

Fig. 6.1 The CEP – CONEP system and its relation to ANVISA

protocols comply with the ethical criteria established in the regulations. The CEPs are multidisciplinary, and must include specialists in health sciences, clinical sciences, statistics, and social and human sciences, with the restriction that members of the same professional category may not form more than half the committee. CEP members are elected for a three-year term; at least half of them are elected by their colleagues, and at least one must represent the users of the institution.

The CONEP is part of the National Health Council (CNS) and receives logistical support from the Ministry of Health, including travel expenses for members coming from different regions and institutions in the country, but administratively it does not report to the Ministry and is independent in decision-making. It consists of 15 members and 15 alternates chosen by the CNS from names provided by the CEPs, and each serves for a period of four years. Six members are selected by lottery, and nine based on their professional expertise. One member must represent health care workers, another the managers, and two members are the users of the National Health System (SUS). The CEP and CONEP coordinators are elected by the committee members.

The CEPs are responsible for the ethical review of all the projects taking place in their own institutions. CONEP examines projects approved by the CEPs that pose major ethical risks and meet the requirements to be classified as special projects, such as research in genetics, human reproduction, international collaboration, biosafety, those involving indigenous groups, and any project the CEP determines that should be evaluated by CONEP.

CONEP is also responsible for maintaining the register and supporting the CEPs, proposing additional regulations, and providing technical assistance. Since 2008, CONEP has the authority to make inspections of the implementation of clinical trials and of the CEPs together with ANVISA.

6.6 Initiating the System and Challenges to the Process

To assure functionally competent CEPs, establish common evaluation criteria, and standardize the decision-making process, CONEP listed the following actions:

1. Develop a national information system – SISNEP, a single data base of information about projects approved by the CEPs and by CONEP, accessible through the internet to researchers, CEP and CONEP members, and the general public. This system has been revised and renamed as Plataforma Brasil, and the general public can access to a subset of the information in the website http://aplicacao.saude.gov.br/plataformabrasil/login.jsf
2. Prepare a manual of procedures for the CEPs, with the participation of ten experienced CEP coordinators
3. Provide technical and financial support to strengthen and educate the CEPs, providing equipment and incentives for the local preparation of courses. This activity was also supported by the Secretary of Science and Technology in the Ministry of Health, which has also invested resources in the training of its members, and by the National Health Council (CNS), which sponsors annual

conferences of committee coordinators to discuss questions arising during the evaluation of protocols and other current concerns

CONEP monitors the performance of the CEPs using various strategies: (1) when they are first formed and they formally request to be recognized as a CEP, and when they renew their permit every three years; (2) by reviewing the annual reports submitted by the CEPs to CONEP, which include, among other important matters, the number and type of projects discussed, the number of meetings for project evaluation and the number of members present at the CEP meetings; and (3) by reviewing the CEP evaluations of special projects which need to be also submitted to CONEP. This double examination of special projects serves to assess the CEPs' compliance with the ethical regulations. In 2003, CONEP instituted a system for annual evaluation, recommending the suspension of committees that did not meet minimum performance levels (see Box 6.3).

Since this system was initiated, CONEP has revoked recognition to between two and 10 % of the CEPs annually. There is no doubt that this system is useful, but it is still not sufficient to ensure their appropriate performance and several proposals for improvement have been made. One of the suggestions is to promote exchange visits between members of different CEPs, but funding is absent. Currently, in compliance with Resolution RDC 39/2008, there are plans to make supervisory and inspection visits to the CEPs, in coordination with ANVISA, but there are problems with the allocation of funding and the training of personnel for this task. So it is still a work in progress, with the goal of establishing a supervisory system with regular and systematic oversight. Meanwhile, only sporadic inspections take place after specific problems requiring the attention of the national agency have been noted.

Box 6.3: CONEP Criteria for the Evaluation of CEPs

- Maintenance of the mandated composition of CEP personnel (Res. CNS 196/96, VII.4, VII.5) including representatives of the users of the system and informing CONEP of any changes that eventually become necessary
- Announcing the CEP decision on projects within the 30-day period proscribed by Res. CNS 196/96, VII.13.b
- Sending a six-monthly report to CONEP of all projects approved during that period
- Participation of more than 50 % of the CEP members in the meetings
- CEP meetings held at least once each month
- Having a designated place and time for the meetings to facilitate participation by researchers and study volunteers
- Maintaining a record of the sessions in an approved file
- Having an adequate, dedicated space to maintain confidentiality of all records and other documents
- Storage space within the institution to keep all CEP administrative documents and those of all reviewed projects for a minimum period of five years

(continued)

Box 6.3: (continued)

- Expectation of reviewing at least 12 projects per year; this estimate is based on projects evaluated in previous years
- When the CEP requests renewal of permission to operate, there must be proof that the CEP has an internal document governing its operation, approved during the first year following its registration
- There must be a designated administrative officer for the CEP, supported by the institution
- The CEP must have a fully equipped office with access to Internet, furniture, telephone, fax and office supplies
- Development of educational materials on research ethics, for CEP members, local researchers, and the community in general

At the end of 2007, 557 CEPs, involving 8,107 people, were operating in the principal research centers of the country. In 2005, CEPs evaluated 17,000 research protocols with a proposed recruitment of 600,000 study subjects. CONEP reviews annually between 1,000 and 1,500 special projects, which is less than 10 % of projects presented to the CEPs, signifying that the CEPs approve more than 90 % of research protocols involving human subjects. The majority of projects reviewed by CONEP involve new medications, and are often multicenter international studies, followed by studies in the area of human genetics, most of which include testing for genetic problems, the search for polymorphisms in certain populations, and the use of stem cells.

6.7 An Evaluation of the System After 12 Years of Experience

Twelve years after Resolution CNS 196/96 was approved, a large number of institutions have supported the CEP/CONEP system, which has facilitated the gathering of information about research involving humans that has taken place in the country, the establishment of a system to protect research participants – specially vulnerable populations, and the development of procedures for the ethical review of the research protocols and for prohibiting or suspending studies that do not conform with ethical guidelines. The system has been institutionalized rapidly, and without doubt has protected human subjects and prevented abuse.

In 1996, the first year of the system, CONEP classified 70 % of special projects that had previously received CEP approval as “opinion pending”. CONEP could not give its final approval to these studies because they did not conform to the regulatory requirements, had missing information, or did not comply with ethical

requirements. The other 30 % applications were approved. Between 1996 and 2002, the proportions were reversed, and by 2002, 70 % of proposals evaluated by CONEP were approved, less than 30 % were pending, and between 1 and 4 % were refused. The most common problems were incomplete protocols, inadequate informed consent forms, incomplete information about the preliminary phases of the study, and inadequate risk-benefit analysis (Freitas et al. 2005). This progression was predictable, and corresponded with the period of training for the CEPs. After 2003, however, the proportion of studies classified as pending, or refused by CONEP, increased. In 2008, CONEP initially approved 45 % of projects, refused 15 %, and classified 34 % as pending, while the remainder did not meet the requirements for review by CONEP (Ministério da Saúde 2009). This apparent regression in the performance of the CEPs reflected CONEP's growing emphasis in minimizing the use of placebos, obtaining guarantees for the continuation of treatment after the completion of study, and requiring insurance policies to compensate participants for the possible adverse effects linked to their participation in the study. Several sources also stated that the CEPs had more difficulty meeting the guidelines and overcoming pressures from researchers and sponsors. These circumstances generated some friction between several CEPs and CONEP, contributed to delays in the process of approving projects (especially those involving new medications), and explained the pressure from the pharmaceutical industry to eliminate CONEP's participation in the review of international projects.

Compared with other countries, according to Hirtle et al. (2000) the Brazilian system of ethical review has several strengths, including the location of the CEPs in the research centers, the legitimacy of the system, the performance of the CEPs, and the attention given to avoiding conflicts of interest.

6.7.1 The Location of the CEPs

In Brazil, the CEPs are located in the institutions where research takes place, and are coordinated at the central level. The large network of institutionally-based CEPs in Brazil inhibits the organization of commercial ethics committees (also known as independent committees), and helps researchers identify the CEP that will oversee the study. The increased presence of commercial ethics committees in other countries in the region is a concern for Brazilians, who think that commercial interest, and the need to satisfy their sponsors, may affect the speed with which they carry out their duties and compromise the safety of the study participants (Lemmens and Freedman 2000). Other advantages of the institutional committees include the following: CEP members have easy access to researchers and study subjects, which facilitates reviewing and monitoring the implementation of research protocols; CEPs can educate the scientific community and the users of the services; they stimulate institutional research and discourage the implementation of isolated studies with little potential to have significant impact in the health of the community.

The legitimacy of the system is of crucial importance because it builds trust in the ethical review. There are two conditions for a system to have legitimacy: (1) the process of forming the ethics committees, and (2) the clear establishment of a locus of responsibility and a decision-making mechanism to govern committee operations. As we have seen, committee members must be democratically elected and include representatives of users of the health system as well as experts in the different disciplines to ensure that the evaluation of study protocols is done with the necessary scientific and ethical rigor. The functions of the CEPs and CONEP are well defined in the resolutions of the National Health Council (CNS), especially in Resolution 196/96, which includes – in addition to guidelines for the ethical analysis of the protocol – the standards that govern a good part of the operational process, which are described in detail in the Manual of Procedures of the CEP.

In practice, the system has some deficiencies. For example, in-depth surveys of 188 people nominated by the CEPs to be part of CONEP revealed the following: more than 40 % of those interviewed said that the representatives of the users of the system participated and contributed little to the discussion of the protocols, and were not invited to provide written reports about the projects; and 10 % reported that meetings took place without a quorum of 50 % of members present (Freitas 2007). This is a problem in other countries also, and shows that support must continue, both to stimulate participation by the general public and to increase the ability of the system to democratize the decision-making processes of the CEPs.

From the perspective of system users, one factor, which threatens the legitimacy of the system is the issue of confidentiality of discussions within the CEPs and the CONEP. These are not public meetings; only the name of the institution where the approved project will be implemented is released, and information about rejected or suspended projects is known only to the CEPs and researchers who are directly involved. This protects the interests of the sponsors, who can move the project to other institutions or countries with less strict regulations. This matter must be discussed thoroughly, as it affects everyone.

6.7.2 Conflicts of Interest

The institutional ethics committee must be independent in its decision-making, and not only assure the protection of the rights and welfare of study participants but also generate public confidence in the system. Many factors influence the independence of institutional ethics committee members, including the role and responsibilities of whoever appoints the committee members. There is concern about the independence of CEPs that serve clinical research groups or institutional groups, which financially benefit from research projects, because pressure may be placed on the CEPs to approve projects that could contribute to the financial or other goals of the institution. For this reason, it is very important to ensure that the ethical review system is totally independent of institutional pressure, which is not an easy task.

Freitas (2007) documented that 48 % of CEP members who had been nominated as candidates for CONEP were holding administrative and management positions in their institutions, and 18 % were directors of the research area, therefore also responsible for increasing institutional research. Most were professionals with research experience, and 26 % had participated in clinical trials sponsored by the transnational pharmaceutical industry.

The Brazilian system does have checks and balances, which help reduce the influence of conflicts of interest and the possibility that sponsors manipulate the institutional CEPs. For example, (1) the CEP-CONEP structure reports and is overseen by the National Health Council (CNS). The CNS is an organization with community participation and social control, and acts as a bridge between the government and the people in general – 50 % of its members represent system users, and 50 % are health care workers; and (2) the CEPs coordinate with a central office – CONEP – which in turn is accountable to the CNS. Other countries with older control systems, e.g. Canada and Germany, say that the lack of a central office has been a weakness of their system and Germany has recently established such an office.

In summary, the Brazilian system has seen continuous development and has tested the ability of the national level to support the process. Much progress has been made although challenges remain. As mentioned, CEP members must not have an administrative appointment in the institution supporting a CEP, must have at least a minimal level of training in research ethics, and must be elected by their peers. The committee coordinator must be democratically elected by the committee members, and the participation of system users must be increased, be it in numbers or in ways to facilitate their active participation in CEP discussions and decision-making.

The system could continue to gain strength if the exchange of opinions and experiences among the CEPs, and between the CEPs and CONEP, was fostered. Greater interaction among CEPs with different levels of experience and development could lessen the pressure on CONEP to guarantee the integrity of the system. These activities should be part of the continuing training and support programs.

6.8 Conclusion

Ideally, clinical trials will increasingly abide by internationally accepted ethical requirements, be focused on the health of Brazilians, and benefit all participants – patients, health professionals, hospitals, universities, and regulatory agencies. Planning and investment in the system is necessary to continue to advance clinical research regulation in Brazil. As Brazil becomes more attractive for clinical research and increases the number of researchers who meet international standards, concern for the respect of ethical standards increases. Current regulations and the creation of the CEP/CONEP system demonstrate that the nation is well able not only to develop guidelines, but also to apply ethical principles through clinical researchers and the hundreds of CEPs that are distributed throughout the country. There is still much to be done, and it is important to reflect on the shared

responsibility of ensuring the sustainability of the system of ethical review of research projects.

It should be noted that the CEP is a legitimate area for democratic debate, and has an important social role from which to draw lessons that according to Gutmann and Thompson (1997) may be applicable to other public policy areas. For example, for endorsing the legitimacy of collective decisions, supporting the value of activities carried out in the public arena, making decisions based on mutual respect when there are different and diverse interests, and also incorporating strategies to permit the correction of errors, on the part of citizens and professionals, which occur when there is an incomplete understanding of the problems that may arise during the planning and implementation of research studies.

References

ANVISA (Agência Nacional de Vigilância Sanitária). 2008. Resolution 39, June 5. http://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2008/res0039_05_06_2008.html. Accessed 28 Oct 2012.

Beauchamp, T., and J.F. Childress. 2008. *Principles of biomedical ethics*, 6th ed. New York: Oxford University Press.

Conselho Nacional de Saúde. 2000. Rules on research involving human subjects. Resolution CNS 196/96 and others. Brasilia: CONEP. http://conselho.saude.gov.br/biblioteca/livros/Normas_Pesquisa.pdf. Accessed 29 Oct 2012.

Dos Reis, A.R. 1990. Norplant in Brazil: Implantation strategy in the guise of scientific research. *Issues in Reproductive and Genetic Engineering* 3(2): 111–118.

Francisconi, C.F., D.L. Kipper, G. Oselka, et al. 1995. Comitês de Ética em Pesquisa: levantamento de 26 hospitais brasileiros (Research ethics committees: Survey of 26 Brazilian hospitals). *Bioética* 3: 61–67.

Freitas, C.B.D. 2007. O sistema de avaliação da ética em pesquisa no Brasil: conhecimentos e práticas de lideranças de comitês de ética em pesquisa (The system to conduct the ethical evaluation of research in Brazil: Knowledge and leadership practices of research ethics committees). Dissertation, Universidade de São Paulo.

Freitas, C.B.D., M. Lobo, and W.S. Hossne. 2005. Oito anos de evolução: um balanço do sistema CEPs – CONEP (Eight years of evolution: An appraisal of the CEPs-CONEP system). Cadernos de Ética em Pesquisa 16. http://www.conselho.saude.gov.br/Web_comissoes/conep/aquivos/materialeducativo/cadernos/caderno16.pdf. Accessed 28 Oct 2012.

Gutmann, A., and D. Thompson. 1997. Deliberating about bioethics. *Hastings Center Report* 27 (3): 38–41.

Hirtle, M., T. Lemmens, and D. Sprumont. 2000. A comparative analysis of research ethics review mechanisms and the ICH Good Clinical Practice Guideline. *European Journal of Health Law* 7: 265–292.

Hossne, W.S. 2003. The power and the injustices of research involving human beings. Interface – Comunic, Saúde, Educ 7(12):55–70. http://www.scielo.br/pdf/icse/v7n12/v7n12a04.pdf. Accessed 28 Oct 2012.

Hossne, W.S. 2006. Bioética – Princípios ou Referenciais (Bioethics – Principles or references). *Mundo da Saúde* 30: 673–676.

Israel, G., and S. Dacach. 1993. As Rotas do Norplant – Desvios da Contracepção (The ways of Norplant-the manipulation of contraceptive methods). Rio de Janeiro: Ed Gráfica CBAG.

Lemmens, T., and B. Freedman. 2000. Ethics review for sale? Conflict of interest and commercial research review board. *The Milbank Quarterly* 78(4): 547–584.

Ministério da Saúde. Conselho Nacional de Saúde. 2006. *Manual operacional para comitês de é tica em pesquisa* (Research ethics committees handbook). Brasília: Ministério da Saúde. http://www.conselho.saude.gov.br/Web_comissoes/conep/aquivos/materialeducativo/Manual_ceps_v2.pdf. Accessed 21 Nov 2010.

Ministério da Saúde. Conselho Nacional de Saúde. 2009. CONEP. Commissão Nacional de Ética em Pesquisa. Disponible en: http://conselho.saude.gov.br/Web_comissoes/conep/index.html. Accessed 20 Nov 2010.

Vieira, S., and W.S. Hossne. 1987. *Experimentação com Seres Humanos* (Experimentation in human subjetcs). São Paulo: Moderna.

Chapter 7
Progress and Challenges of Clinical Research with New Medications in Brazil

Corina Bontempo Duca de Freitas and Bruno R. Schlemper Jr.

7.1 The Current Situation of Clinical Research in Brazil

More clinical trials of new medications are carried out in Brazil than in any other Latin American country. According to Clinicaltrials.gov, 1,397 clinical trials had been registered prior to April, 2010; eight before the year 2000, 1,316 between 2000 and 2009, and 73 during the first 4 months of 2010. In April, 2010, 429 studies (31 % of those registered) were recruiting participants. Most clinical trials in Brazil (922, or 71 %) are sponsored totally or in part by the pharmaceutical industry, while the remainder (29 %) are sponsored by a variety of organizations. An unknown number of the latter group includes clinical trials subcontracted by the industry to intermediary companies, such as Contract Research Organizations (CROs) and universities. Approximately 4.4 % of trials are sponsored by United States federal government agencies, including the National Institutes of Health (NIH). More than half of the registered studies are phase III trials (758), followed by phase II (268), phase IV (218), and phase I (68) (Freitas et al. 2005).

As shown in Table 7.1, the number of clinical trials carried out in Brazil has increased greatly, especially between 2007 and 2008. Phase III studies predominate, but phases I and II studies have also increased. The proportion of placebo controlled studies, although high, has been decreasing. The decline in the use of placebos can be attributed, at least partly, to the leadership of Brazilian bioethicists who have been advocating for prohibiting placebo-controlled trials when alternative therapies are available.

Table 7.1 presents the change that has taken place in clinical trial sponsorship. There has been a decrease in clinical trials financed by USA federal agencies,

C.B.D. de Freitas (✉)
Coordenação de Pesquisa e Comunicação Científica, Fundação de Ensino e Pesquisa em Ciências da Saúde – FEPECS, Brasilia, Brazil
e-mail: corinabdf@gmail.com

B.R. Schlemper Jr.
Medical School, University of West of Santa Catarina, Florianópolis, Brazil

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_7,

Table 7.1 Clinical trials in Brazil, 2000–2010

	2005	2006	2007	2008	2009
Number of registered clinical trials	173	206	203	316	294
Phase I	8	8	11	8	20
Phase II	40	45	41	61	45
Phase III	106	138	100	158	138
Phase IV	23	21	39	61	43
Sponsored by:					
Pharmaceutical industry	151	177	152	217	161
NIH and other USA federal agencies	13	8	7	3	4
Universities/Organizations	14	31	56	109	139
With placebo (in the title)	69	77	83	96	85
Percent of total	40	37	41	30	29
Studies in children (<18 years)	33	28	26	61	72
Percent of total	19	14	13	19	24

Based on Clinicaltrials.gov. Not all entries include information about the phase of the trial or the sponsor, and category totals may not correspond with the total number of studies conducted in a particular year

Table 7.2 Number of communications from ANVISA to Research Centers authorizing clinical trials

Year	Number of communications	Year	Number of communications	Year	Number of communications
1995	30	1999	430	2003	819
1996	80	2000	767	2004	881
1997	180	2001	846	2005	940
1998	394	2002	880		

Source: ANVISA. Medications. Clinical Research. Data on Clinical Research. http://www.anvisa.gov.br. Accessed 5 May 2008. The URL address for the English website is http://www.anvisa.gov.br/eng/index.htm

and an increase in studies sponsored by universities and other organizations. The Clinicaltrials.gov register does not include budget information, and mentions only the total number of study participants to be recruited in the study. It does not specify the number of participants to be enrolled in each country.

The International Clinical Trials Registry Platform (ICTRP) of the World Health Organization also shows an increased number of clinical trials taking place in Brazil. Including clinical trials implemented outside the USA, ICTRP data indicates that Brazilians have participated in 20 % more clinical trials than reported in Clinicaltrials.gov. The ICTRP register does include the same level of detail about the characteristics of the clinical trials, as does Clinicaltrials.gov.

Prior to 2006, the National Health Surveillance Agency (ANVISA) had to grant permission for the implementation of the trial to each health facility taking part in a multicenter trial and had to facilitate the importation of medications and medical devices not marketed in Brazil (generally for phases I, II and III clinical trials). The number of facilities receiving ANVISA authorization increased between 1995 and 2005 (see Table 7.2), and there was also an increase in the number of Brazilian

Table 7.3 Studies presented and approved by ANVISA, 2003–2009

Year	Number of studies presented	Number of studies approved	Percent approved
2003	184	177	96
2004	237	197	83
2005	250	213	85
2006	283	229	81
2007	281	221	79
2008	366	243	66
2009	315	216	69

Source: ANVISA. Medications. Clinical Research. Data on Clinical Research. http://www.anvisa.gov.br. Accessed 5 May 2008. ANVISA has a good English website http://www.anvisa.gov.br/eng/index.htm

researchers participating in multicentric studies. Using data from the National Commission for Research Ethics (CONEP), Freitas et al. (2005) documented that each clinical trial protocol for new drugs (medications and vaccines) reviewed by CONEP in 2004 included on average between four and five research centers.

Since 2006, CONEP analyzes only the protocol sent by the first center to receive ANVISA authorization. This center is designated the coordinating center (Conselho Nacional de Saúde Resolução 2005). Authorizations are then extended to the other centers included in the study. ANVISA registrations since 2006 are therefore by clinical trial instead of by research center. Table 7.3 shows a continued increase to 2008 in the number of clinical trial protocols for new medications or medical devices submitted and approved by ANVISA (although the percent approved decreased).

Between 2005 and 2009, an average of 224 clinical trials were approved each year (70 % of protocols submitted). As discussed in Chap. 6 until very recently, ANVISA did not authorize clinical trials nor the importation of drugs or medical devices not marketed in Brazil without prior approval from the institutional research ethics committee (CEP) and from CONEP. ANVISA's Resolution RDC No. 39 (ANVISA 2008) gave the agency the ability to authorize the initiation of the administrative process for a clinical trial following approval of the study by the first CEP without waiting for CONEP's decision, but participant recruitment can not begin until approval is received from CONEP. This change is expected to accelerate the tasks necessary to begin a clinical trial, but a monitoring system is needed to ensure that sponsors and researchers comply with any adjustments that CONEP might request.

7.2 Advantages of Conducting Clinical Trials in Brazil

Conducting clinical trials in Brazil offers the following advantages to the pharmaceutical industry:

- The availability of patients with different patterns of disease (both infectious diseases typically seen in developing countries and health problems of the high-income countries, such as hypertension, diabetes, and cancer)

- People with few resources to purchase needed medications who are willing to participate in clinical trials
- An ethnically varied population
- A young population – one quarter of the Brazilian population is under 14 years of age, and could participate in pediatric clinical trials
- A high proportion of drug-naïve, potential participants (people who have never taken pharmaceuticals, or who have had minimal exposure to them, and have not participated in clinical trials)
- Large, well-equipped medical centers, where many participants could be recruited reducing the need to include many other centers for the clinical trial
- Trained, frequently multilingual personnel, wanting to participate in clinical trials, and
- Brazil's location allows clinical trials of medications for seasonal health problems to continue when the season in the northern hemisphere has ended

The most important item on this list is the ability to recruit study participants. Brazil is the second market for pharmaceuticals in Latin America after Mexico, and it is estimated that in a population of 190 million people, 40–50 % has no – or limited – access to essential medications (Brazil Brand nd). To ensure a high retention rate for study participants, new recruits into a clinical trial receive special services that are unavailable in the free public facilities of the Brazilian National Health System (SUS), such as transportation to the research center, reimbursement for meals, and additional health examinations (Redfearn 2008).

The ease of recruitment compensates for the, until recently, relatively long time required for regulatory approval of a clinical trial through the CEP-CONEP system. One CRO believes Brazil to be one of the best countries for participant recruitment when patient enrollments are slow in other places (Redfearn 2008).

The ease of recruitment may lead to violations of the ethical principle of justice. When it is not possible to recruit patients in other countries, as stated in the protocol, the sponsor of the clinical trial may easily increase the number of Brazilian participants. This means that the principle of justice could be violated, because, instead of evenly distributing the risks and benefits, a greater number of Brazilians than originally planned would assume the risks associated with clinical trial participation. Compared with other developing countries, more clinical trials with children and more large trials with over 1,000 study subjects are conducted in Brazil (Alvarenga and Martins 2010).

Clinical trials are economical in Brazil because the salaries and honoraria of the researchers and assistants are lower than those of staff in higher-salaried countries, and because the majority of the clinical trials are conducted in the medical facilities of the public health system (SUS). It is possible that the SUS subsidizes the research, because mechanisms do not exist to separate the direct and indirect costs associated with a clinical trial, including staff time given to patient recruitment and to other processes specifically related to the clinical trial.

7.3 The Social Importance of Research: Types of Medications and Studies

In Brazil, the increase in participation in international multicenter clinical trials has not corresponded to an increase in the research areas prioritized in the national agenda of the Ministry of Health (Ministério da Saúde 2008). National research priorities include an evaluation of the effectiveness of new therapeutic interventions; the development of protocols which could include physiotherapy, homeopathy, and acupuncture; ways to increase compliance with treatment for chronic conditions; research and development of medications which could substitute for imported, high cost pharmaceuticals, and clinical evaluation of generic medications. Also of national importance is the development of vaccines for pathologies of strategic interest (yellow fever, meningitis B/C conjugate vaccine, varicella, chicken pox), or of epidemiologic concern (dengue, schistosomiasis, leishmaniasis, tuberculosis, malaria, and HIV/AIDS). Given the diversity of Brazilian ecosystems, the research and development of herbal medicinal products and alternative therapies could have great potential. To develop this research, in addition to investing more resources, Brazil has to improve its systems to patent and commercialize its own products.

According to the research protocols registered with the ICTRP, most clinical trials taking place in Brazil are for chronic diseases with a large worldwide market, such as treatments for diabetes, hypertension, cardiovascular diseases, arthritis, mental illnesses, cancer, and the medicalization of some physiological conditions such as hormone replacement therapy for women and, more recently, for men (WHO.ICTRP nd).

There is little research on other pathologies which are more prevalent in Brazil than in most high-income countries, such as malaria, dengue, tuberculosis, or leprosy (Hansen's Disease). Only 1 % of newly developed pharmaceuticals are for illnesses found mostly in low-income countries (Garrafa and Lorenzo 2009).

Phase IV studies, clinical trials with commercialized drugs, need only the approval of the research ethics committee of the institution, and are not reviewed by CONEP. The principal objective of these studies is to get prescribers to recommend the drug. Each trial may include thousands of participants, and they are causing concern for the following reasons:

1. These clinical trials could endanger participants, especially because a patient in treatment must stop the treatment for a prescribed length of time – wash out period – before being able to participate in the clinical trial. Another problem is the frequent use of inadequate doses of active products in the control group
2. If the study sponsors do not guarantee the continuation of treatment when the study medication has been found to be effective and safe, continuing treatment may increase cost for the individual or for the public sector
3. The cost of these clinical trials results in an unnecessary increase in the final price of the medication. The research agenda of the Ministry of Health includes

initiatives to substitute accessible products for expensive pharmaceuticals and medical devices. One suggested option is to deny approval of Phase IV and non-inferiority trials, especially if they are for medications, which will be more expensive than those currently available

The Kaletra study is an example of an unethical clinical trial, which was reported in the media (Leite 2010). In 2005, CONEP suspended a clinical trial of Kaletra sponsored by Abbott, because it had not been approved through the CEP-CONEP system. That same year, representatives from the Audit Department of the Ministry of Health went to the Graffree Guinle hospital in Rio de Janeiro to investigate a complaint of another clandestine clinical trial of Kaletra. The audit found the complaint to be legitimate. In 2007, the complaint was reviewed by the legal department, and in 2009 it was confirmed that the clinical trial had been conducted without the necessary documents. The study was a single-arm Phase 4 clinical trial, taking place in 10 Brazilian centers, with the objective of adding Kaletra to the medical formulary and to the treatment protocol for patients with HIV/AIDS. It was a marketing study disguised as a research project.

7.4 The Most Common Ethical Issues Related to Clinical Trials

Ethical issues related to international clinical trials, which have been discussed frequently by the research ethics committees and CONEP during their first 10 years of existence, can be categorized as follows (Freitas 2009):

1. Concerning volunteer study participants:
   - Recruitment of participants who are receiving treatment and must abandon it during a *wash-out* period before beginning the clinical trial
   - Placebo group comparison, which leaves patients assigned to this group without access to available treatments
   - Problems assuring the continuity of treatments shown to be helpful during a clinical trial
   - Storage and export of biological material to be used in other studies without obtaining specific permission from each participant in the original clinical trial
2. Concerning the principal investigator:
   - The responsibility of the researchers is usually to recruit patients and to collect data and biological specimens, without contributing to the study design or data analysis. Their involvement in a clinical trial rarely increases their own knowledge and skills
   - The study sponsor analyzes the data and publishes the results, which reverses the usual responsibilities – it limits the researcher's ability to analyze the data, and makes the researcher dependent on the study sponsor

Table 7.4 Projects presented to CONEP by approval status (in percentages), 1998–2008

Outcome	1998	1999	2000	2001	2002	2003	2004	2008
Approved	27	40	59	65	64	50	58	45
Questioned	69	58	38	30	32	45	38	34
Not approved	4	2	3	5	4	5	4	15

Source: CONEP (National Commission for Research Ethics. Comissão Nacional de Éticaem Pesquisa) http://conselho.saude.gov.br/web_comissoes/conep/index.html

3. Concerning the institution where the clinical trial takes place:

   – Contracts are made between the study sponsor or the CROs and the researcher, but many clinical trials take place in public facilities which receive no compensation for expenses caused by the clinical trial
   – Contracts exempting sponsors from responsibility for adverse effects on participants during a clinical trial can result in compensation to those affected having to be provided by the institution where the trial took place

Another problem is the lack of a discussion about intellectual property rights, patents, and issues related to the transfer of technology or commercial potential prior to starting the trial, which means that neither the country nor individuals will enjoy long term benefits from participating in the study.

During the initial years of the CEP-CONEP system (1998–2004), only a small proportion of research proposals (including clinical trials) were rejected (see Table 7.4). In 1998 and 1999, a large proportion, around two-thirds, of proposals approved by the research ethics committees was questioned by CONEP and between 2000 and 2008 this proportion remained relatively stable at 30–45 %. Rejected proposals spiked to 15 % in 2008, but whether the rejected proposals were for clinical trials or for other clinical and epidemiological studies also reviewed by the CEP-CONEP system is unknown.

In 2002, CONEP conducted a study of the reasons for their rejection of 34 research proposals previously approved by the CEPs (see Table 7.5). Nineteen (56 %) were clinical trials. More than a quarter (29 %) of all the studies and more than half of the clinical trials were rejected because they included a placebo group. Placebo control studies were used to study treatments for patients with atrial fibrillation, infections and mental health problems. Some of the placebo controlled studies offered the new medication to patients assigned to the placeb group if it was proven effective at the end of the clinical trial.

The second most frequent reason for the rejection of the study proposal was that previous phases of the clinical trial had not been completed (23 %). In one case, the medication was thought to have more risks than benefits. Another clinical trial was rejected because the proposed intranasal pediatric vaccine had been marketed in a European country and had caused reactions such as facial paralysis, and more studies were required to establish its safety and efficacy. During this review, CONEP discussed the vaccine with the immunization department of the Ministry of Health, and learned that even if the vaccine proved effective, the Ministry did not plan to include it in the calendar of vaccinations in the foreseeable future. CONEP

Table 7.5 Reasons given by CONEP for non-approval of 34 research projects in special subject areas, 2002

Primary reason for non-approval	Number of studies	Percent of not approved	Area of study
Placebo controlled studies of new medications without allowing participants to access treatment of proven efficacy	10	29	Atrial fibrillation, panic syndrome, mania, asthma, head injury, genital warts, ankylosing spondylitis, onychomycosis, psoriatic arthritis, tinea pedis
Previous phase incomplete, clinical or pre-clinical, without a clear indication of effectivity	8	23	Bone marrow transplant for hemoglobinopathies, open study of a medication for schizophrenia, new medication for advanced cancer, the use of latex membrane for pterigium surgery, intragastric balloon, herbal medicines for AIDS, cyto-protectors in patients receiving radiation therapy, intragastric polyethylene strips
Inadequate methods, objectives, and confusing inclusion/exclusion criteria which could invalidate the results	5	15	Genetic polymorphisms in populations, Johrei technique, studies in indigenous populations, environmental factors influencing Leishmaniasis, measurement of alcohol in breath expired by crash victims
Burden on vulnerable populations that could result in exploitation and stigmatization	5	15	Intranasal vaccine discontinued in Switzerland, genetic mapping of incarcerated patients, diaphragm and gel in prostitutes, anticancer drugs in terminal patients, Vitamin A in bronchial hyperactivity in children
Application of diagnostic tests without treatment provision for those found to have a disease	4	12	Insomnia/depression in the indigenous population, genetic studies in carriers of HIV without providing the results to study participants, natural history of urban leptospirosis, gingivitis databank
Commercialization of biologic material	1	3	Purchase of surplus pathology material for shipment abroad
Risks exceed benefits	1	3	Study medication had been shown to be carcinogenic in preclinical studies
Total	34	101	

Source: CONEP (National Commission for Research Ethics. Comissão Nacional de Ética em Pesquisa) http://conselho.saude.gov.br/web_comissoes/conep/index.html

Table 7.6 Reasons given by CONEP for non-approval of 42 research projects in special subject areas, 2004

Primary reason for non-approval:	Number	Percent
Risks exceed benefits, or poor risk/benefit analysis (badly justified studies with placebo, and/or a *wash-out* period)	15	36
Proposal incomplete, too abbreviated, confused, erroneous information	14	33
No participant benefit (epidemiological studies not providing test results to participants, nor treatment if disease is detected; genetic studies not providing genetic counseling	11	26
Inadequate or poorly justified methods	9	21
Exposure of vulnerable population to unnecessary risks	6	14
Lack of guarantee of treatment continuity	4	10
No guarantee of confidentiality of information	4	10
Unjustified storage of biological material for more than five years, or insufficient information about the use and destination of the materials or the establishment of a biobank	4	10
Inadequate, restrictive, or ambiguous compensation clause	2	5
Lack of justification (or insufficient justification) to send biological material abroad, sale of organs	2	5
Other reasons: insufficient information about previous phases of the study, exaggerated financial gain (genome), no technology transfer, studies involving the illegal use of human embryos, drugs previously withdrawn from the market, international study that does not include Brazilian counterparts, a sub-study of a primary study which was not approved, conflicts of interest in the strategy to recruit researchers	8	20

Source: Freitas et al. (2005)
Note: Some proposals were refused for more than one reason, and totals exceed 42/100 %

rejected the study proposal because it did not respect the principle of justice when participants would be exposed to the risks of the clinical trial without any potential benefit for the Brazilian population. The remaining reasons for study rejection by CONEP affected mostly population studies rather than clinical trials sponsored by international companies.

In 2004, CONEP again analyzed the reasons for rejecting 42 research proposals (including some proposed clinical trials), and found similar problems (see Table 7.6). During that year CONEP asked for more information on 60 % of the proposals requesting approval (it is not known how many were for clinical trials) because, among other reasons, the documentation and/or the informed consent forms were incomplete, there was a lack of information about the possible use and exportation of genetic material, or access to treatment following a clinical trial was not guaranteed.

Non-compliance with the administrative process (incomplete presentation of information) and / or ethical principles delays final approval of the protocol and therefore the beginning of the clinical trial. The risk of delayed approval, a delayed trial, and ultimately delayed commercialization of the product should be a strong incentive for the researchers, the CROs, and the research ethics committees to comply with the established guidelines.

7.5 Advances in Ethics Regulations and Their Application in Practice

Brazil is making progress in the development of legal and regulatory frameworks to prevent ethical violations, and civic organizations have contributed to this process by facilitating the unveiling of ethical problems related to clinical trials. One interesting development has been the collaboration between various interest groups, including researchers, civic organizations, public policy personnel, professional organizations, and the CEP-CONEP system. NGOs working with HIV/AIDS patients have been very effective in minimizing the risk and maximizing the benefits to clinical trial participants, by eliminating placebos if a proven treatment already exists, and by ensuring access to effective treatments following the clinical trial.

The regulations require study protocols to include complete information about the number and characteristics of the study population to be recruited, a report of the results of the previous phases of the study, documents showing that the protocol has been approved by the country where the study originated, and the budget. The protocol will not be approved until this documentation is complete.

The regulations emphasize that potential participants in clinical trials understand the risks and benefits inherent in their participation and have all the necessary information for making a free and informed decision, which means that potential participants should have enough time to reflect, pose questions and express concerns. CONEP frequently asks for additional information on the consent form, or for changes in the language style, or may request a summary of the information that can be understood by study participants or their legal representatives. In clinical trials, which are not double blind, there may be a specific informed-consent form for the control group.

The architects of the revised ethical rules in Brazil emphasized respect for the principle of autonomy in obtaining informed consent, and this is reflected in the terms they have selected to express that consent must be informed and freely given. Empirical studies, however, have shown that researchers have not been very sensitive to this process, as they continue to use consent forms filled with technical jargon and a bureaucratic system to obtain participants' consent.

Goldim (2006) studied the consent forms used in the Hospital de Clínicas of Porto Alegre and found that at least 11 years of school were needed to understand 91.7 % of the words in the consent form. Only 16.6 % of adults living in the south of Brazil, the most developed part of the country, had this level of education.

A different study of participants in a cardiology clinical trial showed that 50 % of the study population had not understood the consent form while 33 % had not even read it, signing the form because they trusted the physician's recommendation. Two thirds (67 %) of participants who received a placebo did not understand what this meant; and the lack of understanding closely correlated with their education level (Meneguin et al. 2010). Marodin (2009) found that 71.6 % of the adverse effects identified in previous phases of a study were not shared with either the researchers or the participants in the current clinical trial.

Another study conducted in several European and Latin American countries, including Brazil, found that the process of obtaining free and informed consent was part of a bureaucratic system, functioning more as a legal document to protect the study sponsors and researchers than clinical trial participants (Eulabor 2005).

In addition, difficulty in accessing medications limits the full exercise of autonomy when Brazilians must decide if they want to participate in a clinical trial. Patients value the special attention and free services offered by the research team, and may not fully understand the risks of taking experimental medications.

7.5.1 Continuity of Treatment

Two matters that continue to be discussed in the CEPs, CONEP, and ANVISA, are the continuity of treatment following the conclusion of the clinical trial and the justification for the use of a placebo. The National Health Council (CNS) included in three resolutions (Conselho Nacional de Saúde CNS 1996, 1997, 2008) the obligation to facilitate participants' access to experimental treatment if, according to medical opinion, it had been effective for the patient. It should be noted, however, that some patients have only been able to receive the treatment following a lawsuit.

For example, Kauã de Godoy Chaves Pereita was born in Canoas in August, 2003, with the inherited disease mucopolysaccharidosis Type I, a rare and progressive disorder caused by the lack of an enzyme. Kauã participated in a clinical trial sponsored by the Genzime company of Brazil, Biomarin Pharmaceutical and the Genzyme Corporation, which took place in the Hospital de Clínicas of Porto Alegre between March, 2005, and April, 2006. At the end of the trial, Kauã's mother sued the state of Rio Grande do Sul to continue to have access to the experimental treatment, laronidase. The Court ruled in her favor, and the state accepted the judgment and sued the sponsors of the clinical trial.

The Judge ruled in favor of the state of Rio Grande do Sul, and required the pharmaceutical companies to pay to the state the expenses incurred in Kauã's treatment (78,000 reales, approximately US $37,030 on April 30, 2006). In issuing the ruling, the Judge said (Tribunal de Justiça do Rio Grande do Sul 2007):

> They (the pharmaceutical companies) cannot invite someone to participate in a clinical trial and, after discovering or perfecting a medication, require that the participant sues the state to provide the medication which he or she has contributed to develop

For the Judge, the relation between the participant and the researcher is independent of the state's promise to protect the health of its citizens. The moment that a pharmaceutical company invites a patient to participate in a clinical trial, the company assumes an obligation regarding the risks to which the participant might be exposed. The Judge added:

> It is an obligation arising from the activity undertaken by the laboratory, and cannot be shared with anyone

According to the Tribunal de Justiça do Rio Grande do Sul (2007) the informed consent form stated that:

> Following the 26 weeks of treatment, Aldurazyme (laronidase) will be offered with no time limit to patients who have participated in the study and have not missed more than three consecutive infusions if they were receiving them weekly, or two consecutive infusions if they were receiving them every two weeks

During the past 2 years, CONEP has closely followed the implementation of this standard, although some researchers have questioned whether offering this benefit would put pressure on study participants and are unsure about how to comply with the standard (Deucher 2009). In Brazil, the CEP-CONEP system would not approve protocols, which do not assure access to the medication, or the continuation of the project so that participants in the clinical trial can continue to have access to the treatment. ANVISA has published recommendations related to the obligation to facilitate access to the effective treatment after the completion of the clinical trial (ANVISA 2010). In this document, ANVISA states:

> . . . in cases in which the participant benefits from the medication under investigation, which, in the opinion of the physician, is a better therapeutic alternative, and when there will be no extension of the study after the approved protocol, the Coordination of Research and New Medications (COPEM) section of ANVISA, with the objective of linking the CONEP regulation with the current health law, recommends that the sponsor continues to donate the pharmaceuticals in accordance with the following criteria and procedures:
>
> 1. The sponsor must provide documentation to ANVISA, either annually or at another time period established by mutual consent, of the quantity of medications necessary to continue to treat clinical trial participants
> 2. A medical report explaining the need for continued treatment with the experimental medication for certain patients, specifying the promise of the medical team to continue to treat these patients
> 3. A declaration from the study sponsor committing to provide the medication and to continue to monitor the safety of the patients who continue with the medication
> 4. A declaration from the study sponsor committing to the importation, storage, and distribution of the medication to the research centers, with a commitment to label the imported medication in accordance with special regulations

The ANVISA recommendations incorporate a system to detect and adequately monitor adverse effects. There has not been any progress in adopting this recommendation, however. There are also legal problems, which prevent all Brazilians from accessing medications, which have been tested in the country. In response to the use of the flexibilities included in the Trade-Related Aspects of Intellectual Property Rights Agreement (TRIPS) to increase access to HIV/AIDS medications, some companies have not registered the new product in Brazil, or in other countries that have used similar strategies such as Thailand, creating a new barrier to access.

Ninety-two Brazilian patients participated in clinical trials sponsored by Boehringer Ingelheim to study the safety and effectiveness of tripanavir in patients who are resistant to other protease inhibitors. This drug has been shown to be effective, and is marketed in other countries. In Brazil, it is available only to people who participated in the clinical trial, while more than 2,000 patients who could have benefitted from the drug have no access to it. In 2008, the Public Defender of

the State of São Paulo sued the government to provide tripanavir without cost to a patient (Pereira 2010). As a result, the Ministry of Health had to provide duronavir, which is also effective in patients with resistance to other antiretrovirals, while Boehringer Ingelheim postponed the marketing of tripanavir until July 2010. The current regulatory framework increases the responsibility and involves physicians in ensuring that the rights of patients at the end of a clinical trial are honored. Physicians have to confirm that there is a procedure to guarantee that the patients who appear to have benefited from the experimental treatment will continue to have access and adverse events will continue to be monitored.

7.5.2 The Use of Placebo

For many ethicists, a clinical trial controlled with placebo is not justified when there are safe and effective medications to treat the condition. This is even less so when the only reason for including a placebo is economic. Clinical trials with a placebo-control group are less expensive, because they require a smaller sample size and a less cumbersome infrastructure than trials where the control group is treated with medicines already available in the market. The only conclusion that can be obtained from a placebo controlled clinical trial is that the new medication might be better than doing nothing, but it cannot inform about the overall safety and efficacy of the new medication over those already available (Tereskerz 2003).

In Brazil, the bioethical discussion about the use of a placebo also involves issues related to the principles of equity and justice. The goal is to avoid the double standard caused by using different ethical criteria for countries with different levels of wealth. Researchers and bioethicists have discussed how the relaxation of standards related to the use of placebo increases the risks for the most vulnerable countries and populations (Greco 2003; Garrafa and Prado 2001).

There are frequent debates and discussions among sponsors, researchers, and society in general over the use of placebo in clinical trials of medications and vaccines, especially during the protocol evaluation process. Proponents of different views have expressed their positions in scientific journals (Garrafa and Lorenzo 2009; Greco 2003, 2008), meetings and conferences. In the psychiatric area, debate intensifies around the studies of medications for schizophrenia, depression, and other mental health disorders (Marques 2000).

The NIH-coordinated clinical trial on the use of nevirapine in pregnant women to prevent the vertical transmission of HIV/AIDS during birth illustrates the Brazilian position against clinical trials with a placebo arm. The principal investigator responsible for the clinical trial in the State Employees General Hospital for the State of Rio de Janeiro, in collaboration with the CEP, expressed the need to offer zidovudine (AZT) to the control group instead of a placebo because at that time AZT was known to be 70 % effective in preventing the vertical transmission of HIV/AIDS. His report was received by CONEP, which, in accordance with Brazilian standards, recommended changes to the protocol, including the use of

AZT in the control group, and to the process of obtaining free and informed consent. Overcoming the reluctance of the international sponsors and the NIH, the study was approved with the proposed modifications. This is a good example of the benefits of having clear standards, and well-trained researchers and research ethics committees (CEPs).

Brazilian physicians who are involved with clinical trials must follow the Code of Medical Ethics of the Federal Medical Council of Brazil (Conselho Federal de Medicina, CFM 2009), which supersedes international standards. In September 2009, the CFM revised the Code of Medical Ethics and reaffirmed the restriction on the use of placebo by medical researchers, prohibiting them from:

> . . . maintaining links, of whatever nature, with medical research with human subjects which include the use of placebo when there are effective treatments for the health problem [under investigation] (Conselho Federal de Medicina 2009)

This code became effective on April 13, 2010.

7.5.3 The Influence of Brazil on International Standards for the Use of a Placebo

With the unjustified use of a placebo being limited in Brazil, there were concerns that study sponsors could move clinical trials to other countries with weaker standards. Anecdotal information suggested that studies with more controversial designs were being carried out in low- and middle-income countries, at times taking advantage of weaknesses in local laws and regulations.

We checked our hypothesis by reviewing the clinical trials registered at ICTRP in 2009. Data in Table 7.7 suggest that clinical trials with placebo control are more frequent in low- and middle-income countries where regulations are often less onerous. It is possible that clinical trials in those countries required the use of placebos, but this should be confirmed with more detailed studies.

As discussed in Chap. 2, the World Medical Association (WMA) has regularly discussed the use of placebo and has introduced modifications to the Helsinki Declaration that, at times, severely restricted its use, while other versions are more permissive. According to some bioethicists, the last version of the Declaration (2008) removes the restrictions to the use of placebo that were established in the previous version (2000), and reduces the responsibility of study sponsors, effectively limiting protections for study participants (Greco 2008).

The Brazilian association, concerned about a possible weakening of the articles of the Helsinki Declaration dealing with the use of placebo that had been approved by the WMA in the year 2000, took the leadership and promoted the discussion of placebo controls before, during, and after the WMA meeting in Seoul, 2008. Before the WMA Congress, the Brazilian Medical Association organized a meeting in São Paulo of the WMA Task Force responsible for preparing the revision of the Declaration of Helsinki. The Task Force was composed of members from Brazil,

Table 7.7 Placebo controlled studies registered with WHO by selected countries, 2009

		Protocols including a placebo Percent	
Country	Number of registered protocols	Number	Percent
USA	7,790	791	10.2
United Kingdom	1,233	300	24.3
Canada	1,206	244	20.2
Holland	1,070	180	16.8
France	1,098	193	17.6
Brazil	519	65	12.5
India	607	139	22.9
Mexico	213	72	33.8
Argentina	131	52	39.7
Rumania	171	58	33.9
Peru	267	92	34.5
Russia	267	92	34.5
South Africa	177	59	33.3

Source: Table prepared by authors using the WHO – ICTRP register

South Africa, Germany, Japan, and Sweden. Other participants included directors of the WMA and members of the WMA ethics committees. This was the first time that a meeting of a WMA Task Force took place in Latin America.

Prior to the meeting, the Brazilian Medical Association held a forum about clinical research and the Declaration of Helsinki, which was open to the public. The principal themes were the utilization of placebos and post-trial access to medications for study participants. Participants in the forum included members of CONEP, the CNS, the CFM and professionals involved in research with human subjects. At the end of the meeting, it was decided that Brazil would propose the WMA assembly to keep the year 2000 text of the Declaration of Helsinki. In addition, the CNS had prepared a resolution (Conselho Nacional de Saúde 2008) in favor of removing the explanatory notes that had been appended to the Declaration in 2002 and 2004, and, which, in their view, paved the way for allowing the use of placebo when alternative treatments were available and limited the responsibility of the health services due to participants in clinical trials.

The proposal presented by Brazil to the ethics committee of the WMA was to exclude text allowing possible placebo use from the 2008 revision of the Declaration. Great Britain, South Africa, Uruguay, Portugal, Spain, and the President of the WMA ethics committee voted in favor of the proposal. During the plenary session, however, the proposal from the United States, which allowed studies with placebo in special circumstances, was approved with 99 votes in favor, 17 against, and two abstentions.

The approved modifications to the Declaration of Helsinki of 2008 received a response from the Brazilian delegation. During the WMA assembly, the President of the CFM of Brazil gave the following speech (our translation):

> Esteemed Colleagues,
>
> Today we are here together and at the point of ending two years of work on the modification of the Declaration of Helsinki. This key document is for us the most important manifestation of our commitment in the field of human ethics. There are other documents, which are

part of our tradition, but none have the dimensions, the impact, and the level of acceptance as the Declaration of Helsinki.

The Declaration of Helsinki is a liberating document, which puts the World Medical Association in the forefront of the defense of human rights by demanding that the highest ethical and scientific standards be used when research takes place in human subjects. The Declaration of Helsinki protects not only those who participate in research, but also all human beings because it demands that the results from this research be of quality.

The Declaration of Helsinki, as a protector, keeps the beautiful structure of medicine on a firm foundation, strengthening it to be what it must be - able to offer care based on science and ethical conduct.

This is my message which comes to you from my heart, and I say this without concern for the emotion that I feel, because I cannot understand medicine without compassion or the provision of care unaccompanied by love, and I ask you "What are the scientific reasons that can justify the ethical-scientific use of placebo in research with human beings that have not been discussed by Professor Dr. José Luis Gomes do Amaral and which we are defending in the forum of this Association? What is the scientific evidence for change? Where are the irrefutable voices of scientific knowledge leading us to impose change without having to weaken the structure of our beautiful profession? There is only silence. There are no voices, because this evidence does not exist.

We cannot rest here. Brazil proposes to this illustrious Assembly that, with no scientific evidence to modify, justify, or relax the ethical standards governing the use of placebo in research with human subjects, and with the necessity of maintaining the highest level of our professional ethics in defending human interest - which is the only justification for the practice of medicine - we do not approve the modifications to Article 29 of the Declaration of Helsinki as they have been presented to us by the Director of the World Medical Association, and we retain the professional standing that deserves the respect of humanity.

Signed: Edson de Oliveira Andrade, President of the CFM

Four days after the close of the Assembly, the CFM approved a new standard (Conselho Federal de Medicina 2008) which illustrated the concern of the Brazilian medical community for the safety, protection, and wellbeing of the human participants in research, which reads as follows:

(. . .) WHEREAS the decision in the 2008 General Assembly of the World Medical Association, which took place between 15 - 18 October in Seoul, South Korea, changed Article 29 of the Declaration of Helsinki, to permit, for methodological reasons, the use of placebo when treatment of proven efficacy exists;

WHEREAS there is no scientific evidence to justify the weakening of ethical standards and the use of placebo included in the current amendment of the Declaration of Helsinki;

WHEREAS the Brazilian medical delegates did not approve the changes in the proposed new wording for Article 29 of the Declaration of Helsinki (version 2004) that appears as number 32 in the Declaration approved in the Assembly which took place in Seoul, South Korea;

CONSIDERING the decision made at the plenary session on 23 October, 2008,

RESOLVED: Article 1. It is forbidden for physicians to be involved, no matter what the circumstances may be, in research with human subjects which uses a placebo when an effective and efficient treatment exists for the health problem which is being studied.

In addition, as we have mentioned earlier, the CFM amended its Code of Ethics to incorporate the commitment to avoid the use of placebo.

As a result of the heated discussion during the Assembly and the pressures from the low- and medium-income countries, the WMA appointed a new task force to carefully study the problem, and to consider all methodological alternatives to the

use of placebo and their ethical consequences. The task force is made up of 40 researchers from 11 countries, is coordinated by the President of the Brazilian Medical Association and meets periodically. A concomitant international meeting about the ethics of placebo-controlled clinical trials was organized during the meeting of this task force in São Paulo on February 1–3, 2010.

Garrafa and Lorenzo (2009) have expressed concern because the controversy over the use of placebo may take away from the moral authority of the Declaration of Helsinki, thus nullifying the work of more than 40 years during which it has become the best worldwide reference for clinical research. At the same time, they reaffirmed the importance of using the bioethical statements in the Universal Declaration on Bioethics and Human Rights that protect the wellbeing of participants in clinical trials.

In contrast, the Brazilian Medical Association considered that there had been a significant advance in assuring access to treatment after the conclusion of a clinical trial. Paragraph 33 of the present version of the Declaration of Helsinki (2008) affirms that:

> At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits

Vigilance is necessary to avoid the "or" being used to limit the benefits due to the research participants.

7.6 Challenges to Research Ethics in Brazil

This chapter has presented legal and regulatory advances in ethics and research in Brazil. Leaders at high levels of the scientific community, who are committed to bioethics in research, have facilitated the implementation of regulations. There are no evaluations, however, to show that the system functions as it should. Anecdotal information suggests that ethical control in Brazil is more advanced than in other countries, but at the same time there are problems with the performance of the CEPs – one of the most important pillars of the system – and with the informed consents to participate, which are often neither freely given nor truly informed.

Without rigorous evaluations, it is difficult to prioritize the interventions that could have the greatest impact on the protection of clinical trial participants. To that effect, it is important to establish formal mechanisms to monitor and evaluate how clinical trials are being implemented.

It is rarely admitted, but in low- and middle-income countries most participants in clinical trials could be labeled as vulnerable populations (Schlemper 2007), and Brazil is no exception. The majority of patients are recruited from the Brazilian National Health System (SUS), which serves the low-income population, many of whom have problems obtaining medications. It is estimated that between 40 and

50 % of the Brazilian population is in this category. Garrafa and Prado (2001) report that vulnerability implies a context of "fragility", "unprotected", and "underprivileged", and even of abandonment or neglect. Because of this, clinical trial researchers must see that vulnerable patients receive the additional care they may require.

As part of the structure of the CEP-CONEP system, a register of clinical trials was initiated – the SISNEP, which has pioneered the collection and dissemination of data on research with humans although it did not meet the minimum requirements that, according to WHO, a primary register should have until 2011, when it also was made accessible to the public. SISNEP does not have exact information on the number of clinical trials taking place in Brazil, or on those rejected for ethical reasons. Information about rejected proposals, and the reasons for their rejection, could be an important tool to train those involved in the approval of clinical trials, and, if the information was distributed internationally, it could prevent the implementation of controversial studies in countries with the weakest ethical controls on human research.

The CEP-CONEP system has provided manuals and courses to train CEP members and, although CONEP has the authority to monitor and supervise the CEPs, current controls are mostly based on the information provided by the CEPs and are insufficient to ensure their appropriate performance. There is a plan to do on-site supervision and closer monitoring, however CONEP does not have the necessary funding and is currently exploring the possibility for joint inspections of the CEPs by CONEP and ANVISA (see Chap. 6). Similarly, the CEPs have insufficient resources to adequately monitor the approved clinical trials.

Coordination of the CEP-CONEP-ANVISA system should be strengthened by unifying their criteria and recognizing their complementary role. The fact that CONEP responds to the CNS allows it to operate with a reasonable level of independence in decision-making and protects it against the pressures of lobbies that seek to streamline the evaluation processes and undermine the ethical requirements. Lobbying by the Brazilian Association of CROs, which tried to eliminate CONEP's role in the review of clinical trials, is an example (Redfearn 2008). Little is known about the role of CROs in the clinical trial approval process, or the influence that the type of contract between the researchers and the industry or CROs might have on abiding by ethical principles when conducting clinical research. Unfortunately, all contractual information is strictly confidential, and there is concern that the terms of the contracts might have an influence in adherence to exclusion and inclusion criteria, and in the retention of patients who should have been withdrawn from the studies.

The independence of CONEP and the involvement of organized civil society have distinguished Brazil from other countries, has strengthened the ethical revision of clinical trials, and has protected the CEP/CONEP system from external attacks. Openly or in secret, and while pretending to defend human rights, the companies conducting innovative pharmacological research have tried to destroy the ethical review system established by the CNS to reach their undeclared goal of reducing both the cost and the duration of clinical trials.

To counter the private interests, it is important to support the CNS system of ethical regulation. The decision to increase representation from the users of the public health services and to include an advisor from the health employees in the National Research Ethics Commission has been very successful, and strengthens the CEP/CONEP system (see Chap. 6).

The role of national researchers in the analysis of information generated in Brazil is generally not discussed. There is little information about the adverse effects which occur during clinical trials, or of errors which take place during the implementation of the studies. Regulations are needed to improve access to this information.

In conclusion, we suggest the need to develop options – from the perspective of low- and middle-income countries – to the ethical standards that higher income countries want to impose. Although the region is very diverse, if the experiences of the different Latin American countries could be shared, we might reach agreement on what it means to act with justice and equity, and we could develop ethical standards for the clinical trials conducted in our region.

New medications are certainly needed, but they must be safer and more effective than those already available. For reasons of space we cannot provide an in-depth discussion, but it may suffice to say that regulatory agencies should consider not granting market authorizations for "me too" medications prepared by rival pharmaceutical companies on the grounds that they do not add value to the existing therapeutic arsenal, they reduce resources for research and they expose those participating in the clinical trials to unnecessary risks. "Me too" medications frequently contribute to increasing medication costs because the new product tends to be more expensive than that already available. Ethical and scientific standards should require that products under investigation be compared with existing effective treatments, because the social benefit of human research lies in the identification of the safest and most effective treatment and because doing so would be an expression of respect for human research participants.

References

Alvarenga, L.S., and E.M. Martins. 2010. Biopharmaceutical industry-sponsored global clinical trials in Emerging Countries. *Revista da Associação Médica Brasileira* 56(4): 428–433.

ANVISA. 2008. Resolução RDC 39/2008. http://www.interfarma.org.br/site2/images/Site%20Interfarma/Informacoesdosetor/RE/Pesquisa%20Clinica/RDC%20392008Regulamento%20para%20realizacao%20de%20pesquiss.pdf. Accessed 20 Oct 2012.

ANVISA. 2010. Doação de medicamento após término de estudo clínico. http://www.anvisa.gov.br/medicamentos/pesquisa/doacao_medicamento.htm. Accessed 29 Oct 2012.

Brazil Brand. No date. Brazil medical, pharmaceutical, dental and cosmetics market report. http://brazilbrand.com/brazil_industry_import_export_medical_pharmaceutical_cosmetics2.html. Accessed 29 Oct 2012.

Conselho Federal de Medicina. 2008. Resolução 1.885. 22 Oct. http://portal.cfm.org.br/index.php?option=com_resolucoes&buscaEfetuada=true&resolucoesUf=CFM&resolucoesNumero=1885&resolucoesAno=2008&resolucoesAssunto=&resolucoesTexto=. Accessed 29 Oct 2012.

Conselho Federal de Medicina. 2009. Código de Ética Médica. Resoluçaõ 1931de 2009, Cap. 12, Art. 106 (Code of medical ethics, Resolution 1931 of 2009, Chap. 12, Art. 1006).

Conselho Nacional de Saúde. 1996. Normas Regulamentadoras de Pesquisas Envolvendo Seres Humanos (Regulatory norms for research with humans). http://conselho.saude.gov.br/resolucoes/1996/Reso196.doc. Accessed 29 Oct 2012.

Conselho Nacional de Saúde. 1997. National Resolução 251/1997. http://conselho.saude.gov.br/resolucoes/1997/Reso251.doc. Accessed 11 Apr 2010.

Conselho Nacional de Saúde. 2005. Resolução CNS346/2005. http://conselho.saude.gov.br/resolucoes/2005/Reso346.doc. Accessed 4 Nov 2010.

Conselho Nacional de Saúde. 2008. Resolução 404/2008. http://conselho.saude.gov.br/resolucoes/reso_08.htm. Accessed 11 Apr 2010.

Deucher. 2009. Análise da justiça distributiva no fornecimento de medicações após estudos clínicos no Brasil. Masters thesis, Universidade de São Paulo. http://capesdw.capes.gov.br/capesdw/resumo.html?idtese=20091633002010067P7. Accessed 30 Oct 2012.

Eulabor. 2005. Comparative analysis of their pertinence and application for human subjects protection: Identification of common major problematic issues – Deliverable 3. http://www.eulabor.org/docs/liv3_esp.pdf. Accessed 30 Oct 2012.

Freitas, C.B.D. 2009. Bioética e pesquisa com novos medicamentos. *Comunicação em Ciências da Saúde* 20(1): 75–78.

Freitas, C.B.D., M. Lobo, and W.S. Hossne. 2005. Oito anos de evolução: um balanço do sistema CEPs – CONEP (Eight years of evolution: An appraisal of the CEPs-CONEP system). Cadernos de Ética em Pesquisa 16. http://www.conselho.saude.gov.br/Web_comissoes/conep/aquivos/materialeducativo/cadernos/caderno16.pdf. Accessed 28 Oct 2012.

Garrafa, V., and C. Lorenzo. 2009. Helsinque 2008: redução de proteção e maximização de interesses privados (Helsinki 2008: reduction of protection and maximization of private interests). *Revista da Associação Médica Brasileira* 55(5): 497–520.

Garrafa, V., and M.M. Prado. 2001. Mudanças na Declaração de Helsinki: fundamentalismo econômico, imperialismo ético e controle social (Changes in the Declaration of Helsinki: Economic fundamentalism, ethical imperialism and social control). *Cadernos de Saúde Pública* 17(6): 1489–1496.

Goldim, J.R. 2006. Consentimento e informação: a importância da qualidade do texto utilizado (Consent and information: The importance of the quality of the text used). *Revista do Hospital de Clínicas de Porto Alegre* 26(3):117–123. http://www.ufrgs.br/bioetica/cilegib.pdf. Accessed 25 June 2010.

Greco, D.B. 2003. As modificações propostas para o parágrafo 30 da Declaração de Helsinque 2000 diminuirão os requisitos relacionados ao acesso aos cuidados de saúde para os voluntários de ensaios clínicos (Modifications proposed for paragraph 30 of the Declaration of Helsinki 2000 will reduce the requisites for access to medical care by clinical trial subjects). *Revista Brasileira de Epidemiologia* 6(4): 284–290.

Greco, D.B. 2008. Acesso a tratamento para os voluntários de pesquisa clínica: Direito inquestionável com a perspectiva de expandir para a saúde pública o acesso aos produtos desenvolvidos (Access to treatment for volunteers in clinical trials: An unquestionable right to expand public health or access to new drugs). Caderno Midia e Saúde Pública, 119–130. http://www.esp.mg.gov.br/wp-content/uploads/2009/06/caderno-midia-e-saude-publica-3.pdf. Accessed 30 Oct 2012.

Leite, F. 2010. Estudo sobre AIDS é questionado. O Estado de São Paulo 16 Feb. http://www.estadao.com.br/noticias/geral,estudo-sobre-aids-e-questionado,511916,0.htm. Accessed 11 Apr 2010.

Marodin, G. 2009. Riscos de Eventos Adversos Gastrintestinais nos Projetos de Pesquisa de Fármacos Envolvendo Seres Humanos. Dissertation, Universidade Federal Do Rio Grande Do Sul (Risks of adversed gastrointestinal events during clinical trials in humans). http://capesdw.capes.gov.br/capesdw/resumo.html?idtese=2008242001013018P5. Accessed 30 Oct 2012.

Marques, R. 2000. Grupo Placebo: psiquiatria não é exceção (Placebo group: Psychiatry is not an exception). *Bioética* 8(1): 43–50.

Meneguin, S., E. Zoboli, R. Domingues, et al. 2010. Entendimento do termo de consentimento por pacientes partícipes em pesquisas com fármaco na cardiologia (Understanding of the meaning of consent by patients who participate in clinical trials with cardiology drugs). *Arquivos Brasileiros de Cardiologia* 94(1): 4–9.

Ministério da Saúde. 2008. Agenda nacional de prioridades de pesquisa em saúde (National program of priorities in health research). 2nd ed. Secretaria de Ciência, Tecnologia e Insumos em Saúde. http://bvsms.saude.gov.br/bvs/publicacoes/AGENDA_PORTUGUES_MONTADO.pdf. Accessed 30 Oct 2012.

Pereira, E. 2010. Justiça obriga SP a fornecer remédios a portadores de HIV (Justice rquires SP to provice drugs to HIV patients). O Estado de São Paulo. 10 Jan. http://www.estadao.com.br/noticias/geral,justica-obriga-sp-a-fornecer-remedios-a-portador-de-hiv,107460,0.htm. Accessed 30 Oct 2012.

Redfearn, S. 2008. Trials thriving in Brazil: A quickening process. *ClinPage*. www.clinpage.com/article/trials_thriving_in_brazil/C15. Accessed 29 Oct 2012.

Schlemper Junior, B.R. 2007. Acesso às drogas na pesquisa clínica (Access to drugs during clinical research). *Revista Bioética* 15(2): 248–266.

Tereskerz, P. 2003. Research accountability and financial conflicts of interest in industry sponsored clinical research: A review. *Accountability in Research* 10(3): 137–158.

Tribunal de Justiça do Rio Grande do Sul. 2007. 7ª Câmara Civil, AI nº 70018752733 (The trial took place on Apr 25 2007). http://www1.tjrs.jus.br/site_php/consulta/download/exibe_documento_att.php?ano=2007&codigo=443699. Accessed 29 Oct 2012.

WHO.ICTRP-International Clinical Trial Registry Platform. nd. http://apps.who.int/trialsearch/AdvSearch.aspx. Accessed 29 Oct 2012.

Chapter 8
A Small Country for Big Pharma: Costa Rica

Antonio Ugalde and Nuria Homedes

8.1 Introduction

Costa Rica is a small country (approximately 51,000 km^2; 19,730 sq. miles), with a per capita income of US$6,500 (2009), and a population estimate of 4.5 million people (2009). Half of the population resides in the capital, San Jose. The Costa Rican infrastructure is well developed, and literacy is almost universal.

The Costa Rican Social Security Fund (CCSS) covers about 90 % of the population with comprehensive services that are offered at all levels of complexity, and include catastrophic diseases and pharmaceuticals. All services are free at point of service. It is important to know the history of the CCSS to understand the development of clinical trials in Costa Rica, the evolution of their regulations, and the conflicts that have arisen as a consequence of the trials.

Until the mid-1970s, the Costa Rican health system was very similar to those of other Latin American countries. Medical services were provided by the CCSS and the Ministry of Health (MH), and the latter was also responsible for the provision of public health programs. Businesses had to enroll their employees in the CCSS, and the premiums were paid by the employer, the employee, and State contributions. Non-employed people received health care through the MH. This changed in 1974 when all MH infrastructures were transferred to the CCSS, which became responsible for providing health services to the entire population, while the MH remained responsible for public health and the stewardship of the health sector. At the beginning of the 1980s the CCSS provided all medical services to approximately 85 % of the population. Costa Ricans were proud of having a universal and affordable medical care system and free medications. Mobile medical units

A. Ugalde
Department of Sociology, University of Texas, Austin, TX, USA

N. Homedes (✉)
School of Public Health, Division of Management Policy and Community Health, University of Texas Houston Health Science Center, El Paso, TX, USA
e-mail: nhomedes@utep.edu

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_8,

equipped with a physician, a nurse and a pharmacist made regular visits to all dispersed, rural populations.

Without the responsibility for the delivery of medical care, the MH became an institution of limited functions. At that time, there was little investment in public health services, and most of the health resources were transferred from the MH to the CCSS to cover the costs of the services rendered to those previously served by the MH. Constitutionally, the MH continued to be accountable for regulating the entire health sector, but according to Article 73 of the Constitution, the CCSS was a decentralized autonomous entity and could make its own regulations independently of the MH. While the CCSS decisions could not contradict those of the Ministry, they could go beyond those of the MH. This constitutional ambiguity created conflicts between the two institutions, thus affecting the regulation of clinical trials.

The CCSS had more economic resources, and personnel and political influence than the MH. A large number of CCSS employees were physicians, nurses, and pharmacists – respected professionals – and the Legislative Assembly of Costa Rica, aware of their prestige, traditionally responded to CCSS' interests. The quality of the hospitals and health centers in the CCSS was important for the development of clinical trials; the slow development of the private health sector meant that for many years most clinical trials took place in CCSS facilities.

Contrary to what has been presented in other chapters of this volume, access to pharmaceuticals does not explain the willingness of the Costa Rican population to participate in clinical trials except when there is no approved treatment. CCSS physicians have always had a wide choice of drugs to prescribe, and all the medicines are dispensed free of charge by pharmacists operating in the same facilities where the medical services are rendered.

Costa Rica has an enviable stable democratic history compared with the dictatorships and militarism that prevailed for a long time in many countries of the region. The democratic tradition in Costa Rica has allowed the Legislative Assembly (in collaboration with the general population and the auditors of public institutions) to uncover ethical violations during the implementation of clinical trials, although solving the underlying problems has proven to be more difficult.

Citizens have exercised their constitutionally protected civil rights to confront the authorities and demand adherence to the ethical principles included in the international declarations ratified by the Costa Rican government. The Constitution empowers individual citizens to appeal to the Supreme Court, using a simple and inexpensive process, when they believe that the government has violated basic rights. As will be seen, this process has been successfully used to request documentation about clinical trials that the Minister of Health refused to provide.

Much of the information in this chapter is taken from publicly-available official documents, including reports prepared by the auditors of the CCSS and the National Assembly, Legislative Assembly records, documents from the Office of the Ombudsman, notices and official correspondence from public institutions, and Court decisions, including those of the Supreme Court.

8.2 The Number of Clinical Trials in Costa Rica

Costa Rica was the first country in Latin America where foreign institutions and the transnational pharmaceutical industry began conducting clinical trials. The number of clinical trials implemented in Costa Rica appears small, but it is significant when we consider the size of the country, and the proportion of pediatric trials is particularly impressive. Moreover, in spite of its stable history of democracy and the interest of the Legislative Assembly in the regulation of clinical trials, the total number of clinical trials implemented in the country over the years is unknown. Democracy does not assure bureaucratic transparency, it only provides more tools to uncover it.

The National Council for Health Research (CONIS) was originally created in 1998 within the Ministry of Health, and began to authorize clinical trials and keep a registry in 2003. Nevertheless, the information that is publicly available is very limited, and could be better organized. Citizens cannot obtain reliable information about the number of clinical trials being implemented, the number of participants, the names of the sponsors, or the principal investigators. It is hard to understand why CONIS refuses to provide this information because it cannot be considered an industrial secret. CONIS' information is not standardized and the information from organizations that carry out clinical trials is difficult to interpret. Some report the number of submitted protocols while others the number of approved protocols, and often do not differentiate the clinical trials with medications from those with medical devices or surgical procedures. There have been genetic clinical trials in the National Psychiatric Hospital that have not been differentiated from other studies. Moreover, existing reports do not specify the number of sites involved in the study and therefore a particular trial could be counted multiple times.

The history of clinical trials in Costa Rica dates back to 1962, but at that time, there was no registry and aggregate information is not always available. The data reported here comes from two sources. The number of trials conducted between 1993 and 2004 were estimated by the authors using the records of a lawsuit against the Ministry of Health, and refer to clinical trials that took place in public facilities (that is, the Social Security system, CCSS) and in the private hospital, Clínica Bíblica (see Table 8.1). During this period, 182 clinical trials were conducted with a total of 9,422 participants, and they were sponsored primarily by Pfizer (45), Johnson & Johnson (23), and Merck (20). Companies with fewer clinical trials were SmithKlineBeecham, BristolMyersSquibb, ScheringPlough, Abbott, Amgen, Roche, Aventis, GlaxoSmithKline, Ortho, Bayer, Jansen, Parke Davis, Searle, Upjohn, Wyeth, Pharmacia, Eli Lilly, and other smaller companies.

Table 8.1 does not include the studies conducted in private facilities, other than Clínica Bíblica, which became increasingly relevant in the mid-1990s when the CCSS, for reasons that will be discussed later, became more vigilant, limiting the use of its centers and hospitals for clinical trials. According to a study published in 2006 (Fallas López 2006), CIMA, a private hospital, had completed 23 trials, was conducting 13, and had suspended 11. This source did not specify the number of protocols approved per year, the reason for the suspension of 11 trials, the number of participants, or if the trials involved medications. The private University of

Table 8.1 Clinical trials by year, 1993-July, 2004

Year	Total number of trials
1993	6[a]
1994	14[b]
1995	13
1996	14
1997	13
1998	15
1999	19
2000	22
2001	19
2002	22
2003	12
2004	13
Total	182
Total number of participants	9,422[c]

Source: The National Children's Hospital, 1993–2002; Costa Rican Institute of Clinical Research/ Neeman, 1994–2004; [d]The Pediatric Care Institute, 1994–2004; [d]Hospital Clinica Biblica, 2002–2003; [e]The National Psychiatric Institute, 1996–2002; [e]Hospital San Juan de Dios, 2000–2001

[a]National Children's Hospital data only

[b]The audit report from the CCSS (CCSS, Internal Audit, 1995) is the sole source for 1994 data

[c]Of the 182 clinical trials, 10 had no information on the number of participants

[d]Information only from the years indicated following the names of the hospitals and of the two CROs. It is not known if the two private companies conducted clinical trials before or after these dates

[e]Information only from the years indicated

Medical Sciences, from its establishment in 2000 until 2006, "conducted 216 studies and in 2005 supervised 71 active investigations" (Fallas López 2006). These numbers demonstrate the tendency to transfer clinical trials from the CCSS to private facilities. Today most trials take place in the private sector.

Information about clinical trials conducted between 2005 and 2009 is from clinicaltrials.gov, a federal database that is maintained by the US National Library of Medicine, and does not report the number of participants to be recruited by country. In addition, not all trials implemented in Costa Rica are included in Clinicaltrials.gov, which often excludes the trials that are implemented outside the USA and some Phase I and Phase IV trials (see Table 8.2).

The USA database shows a relatively high proportion of clinical trials involving children, 30 % of all trials registered between 2005 and 2009. The Office of Research and Bioethics of the Center for Strategic Development and Information on Health and Social Security (CENDEISSS, in Spanish),[1] a department of the

[1] CENDEISSS is a Center within CCSS charged with promoting scientific research in CCSS. Its Research and Bioethics unit (which includes the Office of Research and Bioethics and the Scientific Ethics Committee) serves to ensure that the research adheres to the principles of bioethics as set forth in international documents.

Table 8.2 Clinical trials by year, 2005–2009

	2005	2006	2007	2008	2009	Total
Number of registered clinical trials	23	16	13	28	13	93
Phase I						
Phase II	7	2	2	3		14
Phase III	14	12	7	21	13	67
Phase IV	1	2	4	4	0	11
Sponsored by:						
Pharmaceutical industry	21	16	13	28	13	91
NIH and other federal agencies in the United States	2	0	0	0	0	2
Universities and Organizations	1	1	0	1	0	3
With placebo (in the study title)	14	7	4	13	3	41
Pediatric studies, 0–17 years	6	8	3	9	2	28

Source: www.clinicaltrials.gov

CCSS, had previously noted the high number of pediatric trials. In a 2004 report (Subárea de Investigación y Bioética de CENDEISS 2004; Mata 2004), CENDEISSS documented that 44 of 84 trials had taken place in the National Children's Hospital. A CCSS internal audit (Auditoría Interna CCSS 2005:14) found that of all clinical trials financed by external companies between 1988 and 2004 (55), 47 % (26) took place in the National Children's Hospital.

The establishment of Costa Rica as a good country for pediatric trials is largely due to the influence of a pediatrician who was Deputy Minister of Health (1975–1978). The Deputy then became the Director of the National Children's Hospital, and in 1986, was named Minister of Health in Costa Rica (1986–1990). As Hospital director, with the support of the Minister of Health, he organized the Pediatric Care Institute – a Contract Research Organization (CRO) – that operated within the hospital, and one of the physicians in the group became the Director of CENDEISSS; one of CENDEISSS functions is the ethical review of clinical trials that are implemented at the CCSS. This is to say, this physician became the director of the Center responsible for the ethical approval of clinical trials conducted in CCSS facilities and at the same time he was implementing those trials. These conflicts of interest were documented by the Internal Audit Department of the CCSS (Auditoría Interna CCSS 2005).

Another CRO, the Costa Rican Institute for Clinical Research (ICIC), was founded in 1991 and opened a pediatric clinic in front of the National Children's Hospital, where it was easy to recruit subjects for clinical trials. Reports obtained through a court order by the Costa Rican Association of Bioethics, a civic organization, showed that the ICIC conducted 158 and the Pediatric Care Institute 41 clinical trials between 1994 and 2004, and many of them were implemented jointly.

Another pediatrician working for ICIC was Chief of Infectious Diseases at the National Children's Hospital. Her clinical trials were sponsored by Bristol-Myers Squibb, Aventis Pharmaceuticals, Aventis Pasteur, Abbott, Pfizer, and Johnson &

Johnson (Merino del Río 2006). In 2006, she became Minister of Health and was reappointed for another 4-year term by the new Government in 2010.

The high number of placebo-controlled clinical trials is also noted. This is partly explained by several vaccine trials against viral infections, for which there were no other vaccines.

8.3 The Regulation of Clinical Trials

The process for establishing the legal and regulatory clinical trials framework in Costa Rica has been difficult, winding its way for more than 35 years, with many ups and downs, and no meaningful result, as yet. Historical analysis of the regulatory process suggests that four groups in Costa Rica have competed to define regulations for clinical trials: (1) the Ministry of Health, always supported by the Executive Branch of Government, who promoted legislation favoring the interests of research physicians and of the pharmaceutical industry; (2) research physicians, frequently employees of the CCSS, who incremented substantially their salary with proceeds from the trials and wanted to maintain the additional income and fringe benefits that those who conduct research for the industry receive; (3) members of the Legislative Assembly, who opposed the use of public facilities to benefit foreign companies and wanted to protect the human rights of study participants, and (4) CCSS professionals and non-government groups opposed to using CCSS infrastructure (or public infrastructure in general) for the private benefit of research physicians and the pharmaceutical industry. Some CCSS managers, however, have taken positions aligned with the MH, which were questioned by the legal department and the internal auditors of the CCSS.

Appendix 8.1 lists all approved or defeated laws and regulations, and the proposed legislation presented to the National Assembly by Deputies, by the CCSS and by the MH. The General Health Act of 1974 – still in effect – was the first legal document establishing guidelines for the implementation of clinical trials; it stated explicitly that several principles contained in the Declaration of Helsinki should be followed. The Act required the informed consent of study participants or their legal guardians, and guarantees of the scientific quality of the study and its researchers, who had to be from institutions accredited by the MH. The Act prohibited clinical trials that could endanger the participants. This Act was one of the first in Latin America, but it lacked specificity, and left many important aspects unregulated.

The following year, 1975, the MH approved the first "Regulations for Research and Experiments in Human Beings". It established an Institutional Scientific Committee (CCI) to advise the MH on human research and experimentation and to be responsible for the revision and approval of all their protocols.

In 1976, as a result of abuses that will be discussed later in this chapter, a new bill, aimed at complementing the General Health Act with additional ethical principles included in the Nuremburg Code and in the Declaration of Helsinki, was presented to the National Legislative Assembly. Following modification and approval by the

seven-member Standing Committee on Social Affairs (Asamblea Legislativa de la República de Costa Rica 1976), the Legislative Assembly approved the new law and sent it to the President of the Republic for his signature. The President, supported by the Minister of Health, vetoed it (Ministerio de Salud 1976).

The reasons for the veto, given in a brief letter from the President and the Minister of Health to the Legislative Assembly, referred almost exclusively to semantic aspects of Article 64, rather than substantive problems with the law itself. If the MH had been interested in the resolution of the differences between the Executive and Legislative branches, these aspects could have been discussed and resolved. In the absence of a law classifying ethical violations as a crime, the Courts in Costa Rica have said that they are not competent to judge ethical transgressions. In Costa Rica, infringements on regulations are not criminal offenses. According to the internal auditors of the CCSS (Auditoría Interna de la CCSS 2000):

> . . . general criminal law does not contain any statement criminalizing violations of the regulations governing research involving human subjects

It is for this reason that the MH, the physicians who implement clinical trials, and the foreign pharmaceutical industry feel more comfortable without a law because there will be no consequences if the researchers do not comply with existing regulations.

The letter from the President and the Minister of Health ended with the following statement (Ministerio de Salud 1976:2):

> We want to say that the Ministry of Health will examine and prepare. . . changes to the General Health Act regarding this matter [human clinical trials], which will be submitted promptly to the enlightened understanding of the Legislative Assembly

Thirty-seven years later (2013), Costa Rica still does not have a law regulating clinical trials. In 2010, in response to a petition presented by citizens, the Supreme Court prohibited the implementation of clinical trials involving humans until legislation is enacted and illegal actions defined. The Court decision allowed the continuation of trials previously approved in good faith and already underway.

In 1977, one year after the Presidential veto of the 1976 Bill, the Legislative Assembly unanimously approved the preparation of another Bill to regulate clinical trials in humans and addressed certain recurring problems. That new Bill, which was not approved, would have:

- Forbidden experimentation with adult medications and vaccines in children
- Restricted clinical trials to medications for illnesses affecting the population of Costa Rica
- Required that the number of clinical trial participants recruited in Costa Rica is not proportionately greater than the number of participants recruited in the country where the medication is produced
- Required clinical trial sponsors to obtain permission from the MH to conduct the trials
- Required researchers to obtain informed consent.

8.3.1 Rules, Rules, and More Rules: 1998–2005

8.3.1.1 CCSS Regulations 1998

On March 24, 1998, the CCSS approved its own Regulations for Research in the Social Security Institute of Costa Rica (CCSS 1998). The preparation of the final draft of the regulations took two years, and previous versions of the drafts were reviewed by CCSS management and administrative personnel. The Regulations defined the responsibilities of the CCSS, of the directors of CCSS hospitals and clinics where clinical trials take place, of researchers, and of bioethics committees; and it included policies for the protection and indemnity of participants. An entire chapter was devoted to informed consent.

8.3.1.2 Ministry of Health Regulation of 1998

The MH battle to control the conduct of clinical trials continued with the approval – some months after the publication of the CCSS Regulation – of a Regulation for Research with Human Participants. CCSS was not involved in the process of determining the contents of this regulation, despite owning the facilities where most clinical trials were implemented. This document replaced the 1975 regulation.

The first Article in the new Regulation stated that all clinical research should be governed by the Declaration of Helsinki and the Guidelines for Best Clinical Practice of the International Conference on Harmonization (República de Costa Rica 1998). However, the new regulation was criticized for not incorporating the principles of the Declaration of Helsinki in the remainder of the document. For example, Article 11 required: "... legal and financial insurance for the researcher and his team, for claims arising in the study that are unrelated to negligence or malpractice", but there was no requirement for an insurance policy to cover a participant in case of negligence or illness or death caused by the use of the tested medication as required by the Declaration of Helsinki. This omission became important as the implementation of clinical trials transferred to the private sector where the risks to participants were perceived to be greater, since private facilities and their personnel were not subjected to minimum quality standards (Fallas López 2006).

The Legislative Assembly objected to the MH Regulation for procedural reasons. One objection related to the participation of people with ties to the pharmaceutical industry in the drafting of the Regulation. The accusations were so serious that the national Ombudsman recommended that the Minister of Health revise or rescind approval of the document, but this did not happen until 2003 (Cambronero Castro et al. 2001a). The CCSS Institutional Committee on Bioethics and Research also spoke against the MH Regulation (Auditoría Interna de la CCSS 2000:15):

> ... because it [the 1998 document] allegedly violates human rights, it does not protect the dignity of those involved, it proposes an ethics committee without community participation and without including the cultural values of society, it establishes an advisory body and empowers the institutions that conduct clinical trials to authorize and supervise the implementation of

> clinical trials. . . contravening the bioethical standards approved by the medical community, it establishes public and private committees with the authority to approve clinical research to be conducted in the CCSS

The MH Regulation also created the National Council for Health Research (CONIS), and required all institutions involved in clinical trials to establish Scientific Ethics Committees (CECs) – which later became Institutional Scientific Ethics Committees (CECIs) – and that the committees be accredited by CONIS. In 2004, there were seven CECIs.

8.3.1.3 CCSS Regulation of 2001

In 2001, CCSS approved a new Regulation for Clinical Research in the Social Security Services of Costa Rica (CCSS). The new normative paid very careful attention to the protection of participants through the creation of a Scientific Ethics Council for the entire CCSS and three committees to ensure compliance with ethical standards in special populations – one for children, minors, and pregnant or lactating women; one for adults, and the third for other vulnerable groups. The new Regulation conformed to international recommendations for research involving humans, carefully regulated informed consent, and integrated the new content without contradicting the 1998 Regulation (Oconitrillo and Fabio 2002).

8.3.1.4 Ministry of Health Regulation of 2003

In 2003, the Ministry of Health repealed the 1998 Regulation by Executive Order, and the new policy transferred responsibility to the Institutional Scientific Ethics Committees (CECIs) of public and private institutions and to CONIS. The CECIs were responsible for protecting the human rights of study participants, for approving study protocols, and for supervising the conduct of the trials.

8.3.1.5 CCSS Regulation of 2005

The conflict between the Ministry of Health and the CCSS erupted again in 2005 when the CCSS approved a new Regulation for Biomedical Research in the Social Security Services of Costa Rica – still in effect. The new regulation created Local Bioethics Committees (CLOBI) in CCSS health centers and hospitals. One of the CLOBI's functions was to monitor the studies it had approved. An evaluation of CLOBIs in 2009 showed a series of problems and a lack of capacity to implement the tasks assigned in the regulation. Other deficiencies in the implementation of trials included (CCSS 2009):

- Starting clinical trials and collecting information before receiving approval of the CLOBIs
- Changes in protocols without authorization, for example, changes in sample size and of the inclusion or exclusion criteria

- Absence of quarterly and final study reports
- Insufficient time for CLOBI members to complete their assigned tasks
- The fact that some CLOBIs had incomplete or outdated registration documents, and did not have operating manuals or continuing education programs. Some CCSS facilities did not understand the purpose or activities of the CLOBIs.

The new CCSS regulation prohibited Phase I or II clinical trials in pregnant women and children, but since these trials were not forbidden in the MH regulation, the pharmaceutical industry could conduct these studies in private facilities. A positive aspect of the CCSS regulation was the requirement to obtain a policy from the National Insurance Institute – before receiving authorization for the study – to compensate study participants for harms associated to the clinical trial.

8.3.2 Institutional Conflicts

Lack of space prevents a detailed account of the characteristics of the conflict between the CCSS and the MH. It is important to note that this is not a conflict between two institutions, because, as it has been mentioned, the CCSS has had managers and physicians who conducted clinical trials in CCSS facilities and whose interests were better protected by the MH. The conflict is between two opposing positions, one clearly supported by the MH and the other by civil society groups and CCSS professionals who promoted and defended CCSS interests and wanted to prevent the violation of patients' rights and the use of CCSS resources for the benefit of a few.

Reports from the CCSS Legal Office and the CCSS internal audit department – two independent and presumably unbiased sources – confirmed that researchers used CCSS resources without reimbursing the expenses, left study participants unprotected, and frequently disregarded ethical principles. For example, both sources objected to CROs having access to patients' clinical records, which was considered to be a breach of privacy, and criticized the export of biological samples without ensuring that patients understood how the samples were to be used and who would benefit from them.

The CCSS internal audit reports documented the internal conflicts within the CCSS during the 1990s and the early 2000s, including the opposing views of some board members and how they influenced the changes in the Regulations. According to Acchío Tacsan (2008), several people confirmed that the 2005 Regulation represented the views of CCSS professionals who opposed the implementation of clinical trials in CCSS facilities for the benefit of researchers and the private industry. Members of the Legislative Assembly and civic organizations such as the Costa Rican Association of Bioethics – established during the years of conflict – also protested the use of CCSS infrastructure and the absence of legislation to

protect patient rights. However, none of these groups was against the implementation of clinical trials, and even less against scientific research.

One example of abuse committed by CCSS directors in favor of researchers was the case of the Director of CENDEISSS who gave the Director of the Bioethics and Research Unit of the CCSS a leave without pay in order for him to become full time Dean of the Autonomous School of Medical Sciences in the private University of Medical Sciences. At the same time, this person was the principal investigator in at least two on-going clinical trials at the Costa Rican Institute for Clinical Research (ICIC). The University of Medical Sciences received 216 clinical trial protocols between 2000 and 2006. One member of CONIS said (Fallas López 2006:194–195) that there were two private Ethics Committees which:

> . . . have facilitated the business of transnational companies and have contributed to their development in relative tranquility, even with good conscience. The most important is that of the University of Medical Sciences

In 1999, to minimize the protests of CCSS professionals who objected to the abuses and ethical violations in many clinical trials, the Director of CENDEISSS closed down its Bioethics Unit, saying that the regulation of clinical trials was not a function of CENDEISSS, but the responsibility of the MH and of the hospitals. CCSS legal consultants considered this action of the Director of CENDEISSS inadmissible, since the Constitution granted the CCSS political and administrative autonomy, and it therefore had the capacity to issue its own regulations.

There is sufficient information to show that the MH was interested in favoring the interests of the researchers and the pharmaceutical industry. The role played by the pediatric ministers has been described, but other ministers were also involved. For example, according to a report from the National Legislative Assembly, the Minister of Health, during the 2002–2006 administration, was one of the principal supporters of the Epidemiological Project of Guanacaste discussed in Chap. 9.

8.3.3 More Failed Proposals in the Legislative Assembly

Appendix 8.1 lists the bills to regulate clinical trials that have been proposed by different deputies to the Legislative Assembly in 2000, 2002, 2003, and 2004, and by CONIS and the CCSS in 2005. All of them failed to be adopted. The defense of the interests of the CCSS by deputies and the conflict between members of the Assembly and the MH over clinical trials can be read in reports of the Assembly. A deputy's letter, sent in 2006 to the President of Costa Rica, states that the newly appointed Minister of Health held positions in the CCSS while she was conducting clinical trials for pharmaceutical companies (Merino del Río 2006). Citing an audit of the CCSS, the deputy's letter explained to the President that the results of the studies implemented in CCSS facilities were not reported to the CCSS because, according to the Minister, they belonged to the pharmaceutical companies, and had to be kept confidential until they were used in the applications for market authorization of the

new products. The letter charged that the Minister, during her clinical trials, "had improperly utilized CCSS public resources" (Merino del Río 2006:3). According to the deputy, this led five other deputies to request in 2005 that the Comptroller General of the Republic open an investigation.

According to the CCSS audit (Auditoría Interna de la CCSS 2000), the foreign companies had paid US$ 45 million for the Phase III trials conducted in the CCSS until 2000. When employees of a public entity use a public entity for private benefit, the law requires them to legalize contracts with the Comptroller of the Republic and the contracts between the pharmaceutical industries and the principal researchers were not legalized. In this case, this law would have included the Minister of Health's contracts from 2006 to 2010. The deputy's letter mentioned official communications from other deputies requesting an investigation into alleged legal violations committed by the Minister; for example, she had not obtained an insurance policy for two of her clinical trials.

The lack of transparency at the MH was corroborated when in 2009 a citizen had to lodge an appeal to the Supreme Court to obtain a clinical trial protocol. The Court had to issue three resolutions and six requests to the Minister of Health to get her to comply with the Court order (Collado Martínez 2010). Finally, almost 300 days later, the Minister of Health delivered the protocol after receiving the following warning from the Court (Sala Constitucional 2010):

> For the last time, María Luisa Ávila Agüero, in her position as Minister of Health, is ordered to deliver to the petitioner a copy of the protocol for the study of the AH1N1 influenza vaccine, sponsored by Novartis and approved by the ethics committee of the University of Medical Sciences (CEC-UCIMED, a private university), within twenty four hours from the reception of this order under notice that administrative proceedings against her will be filed in case of non-compliance

Following the Supreme Court decision in 2010 to prohibit clinical trials in Costa Rica, until they are regulated by law, civic groups, the Legislative Assembly and the Executive branch of government are preparing new bills. By November 2013, the Assembly continued to discuss different proposals.

So far, this chapter has reported the failed attempts to enact a law for the protection of human research participants. During these years (1975–2012), several ethical violations have been documented. Other examples are reported in the following section; and, Chap. 9 tells the story of the clinical trial of the HPV 14–16 vaccine, notable for the large number of low-income female participants involved over a long period of time.

8.4 Questionable Clinical Trials

8.4.1 The Early Years: 1962–1990

In 1962, Louisiana State University (USA) and the MH of Costa Rica signed a contract and established the International Center for Medical Research and Training

(ICMRT), financed by the National Institutes of Health (NIH) of the USA. Four years later, following restrictions on the use of NIH funds imposed by the USA Senate, the NIH withdrew from the program, but the ICMRT continued its clinical trials with financing from foreign pharmaceutical companies. According to Trejos (1986), some of the incentives for the pharmaceutical companies to conduct clinical trials in Costa Rica were low costs and the low risk of "legal claims for ethical misconduct related to this type of research" (Trejos 1986).

Trejos reports that in 1974 and 1975 Merck-Sharp-Dohme (MSD) financed 79 % of the ICMRT budget, and ICMRT enrolled 34,000 participants in clinical trials for two formulations of three different strains of influenza virus. One of these had been discontinued in the United Kingdom, by the same MSD, because it had caused "inconvenient" reactions. Twenty-five thousand doses of the same lot that had been discontinued in the United Kingdom were used in Costa Rica without permission from the MH. The vaccine was intended for adults, but in Costa Rica it was given to 20,000 school children without their parents' permission (Trejos 1986).

A study conducted by the University of Costa Rica with a statistically significant sample of those who had received the vaccine found that 70 % of the children had local and systemic reactions. The Director of the ICMRT stated in an interview that the children had been vaccinated in error. When the MH learned of these violations, the only response was to require the ICMRT to obtain advance authorization before conducting clinical trials. In Costa Rica, this vaccine was tested at a proportion of the population of 17,000 people per million, while in developed countries, the ratio was 35 per million (Trejos 1977).

In 1976, the Ministry of Health approved a clinical trial for a measles vaccine, and the vaccines used in the trial had expired 7 years earlier. The Ministry also approved the trial of another vaccine against the respiratory syncytial virus (RSV), a pulmonary illness, affecting children residing in temperate zone countries during the cold months. These two vaccines were given to children in poor neighborhoods in the capital city of Costa Rica. The RSV vaccine was given to a greater number of children than authorized by the MH, and written consent was not obtained from the parents of the children (Trejos 1977).

Once informed of these ethical violations, the National Children's Trust (PANI in Spanish) and a group of professionals initiated a lawsuit against IMCRT for non-conformance with the General Health Act and the Declaration of Helsinki. The court declared that ethical violations were not considered crimes in Costa Rican law, and acquitted the defendants.

The documents presented as evidence during the trial of IMCRT and the investigation undertaken by the Legislative Assembly confirmed that there had been violations of fundamental ethical principles. The Legislative Assembly also found that the Committee for Ethics in Research, which had approved the protocols, had ignored other ethical principles and was not independent – the ICMRT had nominated its members, including members of the research teams, and they received payment for each reviewed protocol (Trejos 1977).

8.4.2 The Last 20 Years: 1990–2010

For several years, two Contract Research Organizations (CROs) conducted a large number of clinical trials in Costa Rica – the ICIC, established in 1991, and the Pediatric Care Institute, established in 1993. Ten years after these CROs had been established, there were five national CROs acting as intermediaries between pharmaceutical companies and physicians who recruited study participants and for doing so "were paid many millions" (Cambronero Castro et al. 2001b).

The first president of the ICIC was a CCSS employee, who signed a contract with the CCSS to conduct clinical trials in its facilities and with its patients. The CCSS Legal Office considered the contract invalid due to irregularities. The ICIC stated that it would organize a Committee for Research Ethics and Science, which was active from August, 1992 to December, 1993. Then the ICIC president contracted with an ethics committee in the USA, but it did not become functional until December 1994 (Auditoría Interna de la CCSS 2000).

In 1995 (see Appendix 8.1), approval for clinical trial protocols was transferred to the Ethics and Science Committees (CECs) of the facilities where trials were to take place, but the CECs of the two principal hospitals of the CCSS refused to approve trials due to possible legal consequences. The directors of the two hospitals stated that approval of clinical trial protocols was a responsibility of the health authorities. The situation became even more complicated when the Inter-institutional Scientific Committee of the MH, which was responsible for the approval of clinical trials before sending them to the public or private health centers, ceased to function in May 1994.

The CCSS auditors reported that, of the 35 clinical trials conducted by the ICIC between 1991 and 1995, at least seven had taken place without approval from any ethics committee, and that a further seven trials had not submitted any information to the CCSS (Auditoría Interna de la CCSS 1995:17–19). In addition, they concluded that the MH had no control over clinical trials until July 1995, and described other ethical violations such as the lack of confidentiality of patient records, the implementation of clinical trials by the Pediatric Care Institute in the National Children's Hospital without authorization from the legal office of the hospital, and the use of public resources without adequate compensation. They also questioned the validity of the informed consent, since the documents were never submitted to the CCSS, and the medical staff in the hospitals where the clinical trials were taking place had no knowledge of their existence (Auditoría Interna de la CCSS 1995).

The situation of clinical trials in Costa Rica from 1995 to 2000 was described in an article published in the Washington Post. The article noted that although Costa Rican law gave the MH the right to inspect clinical trials in progress, none had been carried out due to the lack of inspectors (De Young and Nelson 2000).

The FDA rarely inspected clinical trials in Costa Rica. Between 1995 and 2000, the FDA made six inspection visits, but never shared the results with either the MH or the CCSS. The article in the Washington Post provides some details. For example,

during the inspection of a clinical trial studying the antibiotic meropenem of Merck in the National Children's Hospital, the FDA found that some amount of the medicines needed for the trials were not available, dates were entered in the records retroactively, data were reported without supporting information, and that in several cases informed consent was obtained after the drug had been administered to the child (De Young and Nelson 2000). An FDA inspection of an ICIC clinical trial for the antibiotic Trovan (Pfizer) found discrepancies in documentation, inconsistent records, and that the X-rays for half of the almost 200 participants were missing (De Young and Nelson 2000).

In June 2000, a CCSS auditor identified similar problems in the National Children's Hospital and other CCSS hospitals and clinics (Auditoría Interna de la CCSS 2000). Two years later, a group of professionals founded the Costa Rican Association of Bioethics; they had been frustrated because after the publication of four executive orders between 1975 and 2000 nothing had happened (see Appendix 8.1), there was no adequate regulation of clinical trials to protect participants.

This Association has played an important role: its members have been able to access clinical trial protocols, and have required study sponsors to comply with the Regulations and obtain insurance that would properly compensate study participants in the case of suffering adverse reactions, illness or death resulting from their participation in a clinical trial. The organization also questioned the protocol approvals given by some CECs, and pressured the government and researchers to comply with ethical principles established in international agreements (Asociación Costarricense de Bioética 2004).

8.5 Discussion

In Costa Rica, the implementation of clinical trials is concentrated in the hands of a small number of researchers. For example, one of the members of the Board of Directors of one CRO directed 50 clinical trials, or 27 % of all the trials that took place in the country from 1993 to July 2004, and the Director of another CRO was responsible for 24 trials (12 %) during the same period. Four pharmaceutical companies sponsored more than half of these trials, which presumably resulted in close relationships among a few researchers and transnational pharmaceutical companies. These relationships enhance the professional status of the researchers and since several have occupied important positions in the MH and the CCSS they have good access to health policy makers. From this advantageous position, clinical trial researchers have a significant influence in the regulatory process.

In early 2010, the Supreme Court ruled that new clinical trials could not be authorized in the country until the National Assembly enacted legislation regarding clinical research involving humans. From then at present (November 2013), the Assembly has discussed several bills and amendments without gathering enough votes for their approval; the legislation under discussion represents both the interests of industry and researchers, and the views of those who emphasize the

ethical principles and protection of participants' human rights. During this lengthy process the prestigious clinical trial researchers have lobbied and made public pronouncements (Mohs 2012; Arguedas 2011).

The value and contribution of those who implement clinical trials designed by transnational pharmaceutical companies has been questioned in Costa Rica, and authors have wondered if the professional prestige accorded to these researchers is warranted. In 2006, Fallas López pointed out that the work of researchers contracted to conduct clinical trials is not a scientific endeavor because they do not participate in protocol development or in the data analysis of multicenter studies. He explained (Fallas López 2006:192–196)

> Health professionals who become researchers move from their field of specialty to another where they do not make any significant contribution, but extract significant economic benefit... those involved in... [clinical trials] in the country are mere recruiters [of participants], interested less in the progress of health sciences than in the growth of their bank accounts... not only because in general they do not have a solid scientific background and, consequently, lack expertise and are unable to write... the companies [pharmaceutical companies] must think we are a paradise for research - almost a Banana Republic - no one interferes, not the law, not the authorities...

The author continues by saying that these physicians use their professional position and the confidence and vulnerability of their patients to turn their patients into guinea pigs for the benefit of the multinational companies.

CROs have been characterized as *maquilas*[2] (Fallas López). This is to say, the CROs receive a product (the protocol) which they transform into data, although there is no strategy to verify (as quality control procedures of a true factory) if the process ends in a product of quality or if parts of the process have been manipulated. The use of the term *maquila* is not unreasonable since one of the CROs, the ICIC, is incorporated as an exporting company in the free trade zone of Costa Rica, because in the words of its founder and Director "we export intellectual property" (Rodríguez nd).

Most physicians who take part in clinical trials receive, in addition to a large payment for each patient who becomes a trial participant, other fringe benefits. The pharmaceutical industry supports the travel of researchers and prestigious physicians (Lakoff 2006) to international conferences where they may influence the prescription habits of their colleagues. Without industry support, few Latin American physicians could attend international congresses outside their region. Trips to present data from clinical trials are customarily entirely paid by the pharmaceutical firm. From 1993 to 2004, the leading researcher of the Pediatric Care Institute presented the results of "his" studies in Acapulco in 1993, Quebec and Monterrey (California) in 1995, Hong Kong and Lisbon in 1996, Lausanne in 1997, Kuala Lumpur in 1998, Noordwijk (Holland) and Toronto in 2000, Istanbul, New Orleans,

[2] In Spanish *maquila* means an assembly plant in a low or middle income country, to which foreign materials and parts are shipped and from which the finished product or a part of a product is returned to the original market, and taxes are paid only for the added value.

and Chicago in 2001, Sicily and Chicago in 2003, and San Francisco, Tampere (Finland) and Washington D.C. in 2004.

Undoubtedly there are very skilled physicians in Costa Rica conducting clinical trials, but it is well known that the pharmaceutical industry influences the content of the study reports and the presentations made at conferences, which they use to promote their products. We have not found evidence that clinical trials originating in Costa Rica have had a major impact in the development of medical science in the country.

8.6 Conclusions

The number of clinical trials in Costa Rica is small, but this statement needs to be qualified by the small population of the country, and the fact that several clinical trials involving vaccines have included thousands of participants. A very large number of participants in the trials are children, adolescents and the poor, all of whom fall under the category of vulnerable populations.

Since the abolition of the Armed Forces in 1949, Costa Rica is a country with a solid democratic and participatory system. An easy process allows any citizen to access the Supreme Court and present his/her demands. This process was successfully used to stop the authorization of clinical trials in the country in 2010.

Our analysis shows that during many years, most clinical trials were implemented in CCSS hospitals; these are public institutions that provide medical care for most of the population. It has been shown that the CCSS was not reimbursed, in all or in part, for the expenditures incurred during these trials. The CCSS is funded by the beneficiaries, employers and in a small part, by the Government, which covers the premiums of the indigent. It is not surprising that civil society objected to foreign pharmaceutical corporations, and a few principal investigators and local businesses benefitting from the limited resources of the CCSS. As presented in this chapter, the MH has remained during many years under the leadership of professionals who have been involved in the implementation of clinical trials. Not surprisingly, they have tended to support the pharmaceutical corporations.

The response by the pharmaceutical industry to the barriers imposed by the CCSS was to move the clinical trials to the private sector, including private universities, and private hospitals and health centers where the same physicians who work at the CCSS would recruit CCSS patients directly or indirectly (in private centers located across the CCSS health facilities), illegally using the medical histories of the CCSS. Most private groups do not have the medical technology available in CCSS facilities, which might need to be accessed in case of adverse reactions.

These conflicts of interest help to understand the large number of failed bills to regulate clinical trials and the race between the CCSS and the MH to issue contrasting regulations to control their implementation. The powers granted to

CCSS by the Constitution makes it difficult for the MH to object to or interfere with the decisions made by the CCSS. Civil society has been active in promoting the protection of the human rights of clinical trial participants, but it cannot be affirmed that their efforts have resolved the ethical violations of clinical trials. Due to the small size of Costa Rica's economy, the resources of civil society are very small when compared to those of the sponsors of clinical trials. The contest becomes even more uneven when local businesses such as CROs, private universities, and locally prestigious principal investigators – all of whom make enormous profits by national standards from the trials– join forces to lobby decision makers.

Even if there are many unresolved problems regarding clinical trials in Costa Rica, civil society has been able to stall the implementation of clinical trials and has elevated the discussions that have taken place within the Legislative Assembly, in the media, and during university forums. During half a century, the National Legislative Assembly has failed to introduce a bill that would protect the human rights of those who participate in clinical trials, in accordance with the internationally accepted ethical principles, but it is very likely that the efforts and activities by concerned citizens will continue.

Acknowledgment We thank Dr. Hernán Collado for sharing and facilitating access to the documents cited in this article.

Appendix 8.1: Most Important Clinical Trial Legislation, Regulations, and Bills

1974. The General Health Act contained the first legislation related to clinical trials.
1975. An Executive Order from the Ministry of Health approved the Regulations for Research and Experiments on Human Subjects, establishing an Institutional Scientific Committee (CCI) to approve protocols for research with human subjects.
1976. A Deputy to the National Legislative Assembly presented a Bill to modify the General Health Act, bringing it into conformity with the Helsinki Declaration and the Nuremberg Code. The legislation failed.
1977. The Legislative Assembly approved a Bill to prevent abuses taking place in the country. The Bill failed to become a law.
1995. By an Executive Order, the Regulations of 1975 were amended to create a Scientific Committee in each hospital to support the work of the CCI.
1998. The Social Security Administration (CCSS) approved its own Regulations to govern clinical trials with human subjects carried out in its own facilities.
1998. The Regulations for Research with Human Subjects were approved by an Executive Order. These Ministry of Health Regulations established the National Council on Health Research and the Ethical and Scientific Committees (CEC) in public and private institutions.

2000. The Ministry of Health published standards and procedures for approval, control, and monitoring of research involving human subjects.
2000. A Deputy presented to the National Legislative Assembly a Bill titled "A Law on experimentation in humans subjects, human genetic modification and cloning." The legislation failed.
2001. CCSS Regulations in accordance to international regulations on research with humans and to govern informed consent.
2002. A Deputy presented to the National Legislative Assembly a Bill titled "A Law to govern research and experimentation in human subjects." The legislation failed.
2003. An Executive Order repealed the 1998 Regulations and approved a new Regulation to provide more detailed governance for research with humans and the CCIs. The new decree re-established the National Council on Health Research (CONIS) and the network of Ethical and Scientific Committees (CECs)
2003. The CCSS approved new Regulations, which were in place until 2005.
2003. Deputy Joyce Zurcher presented to the National Legislative Assembly a Bill titled "General Law of bioethics." The Bill was not approved.
2004. Two Deputies presented to the National Legislative Assembly a Bill titled "A Law to regulate scientific research with human subjects." The Bill was not approved.
2005. CONIS presented to the National Legislative Assembly a Bill titled "Comprehensive reform of the General Health Act 5395 and its amendments." The Bill was not approved.
2005. The CCSS drafted a Bill titled "Law on research with human subjects." The Bill was not approved.
2005. The CCSS approved Regulations for biomedical research in the welfare services of the CCSS, with the objective of controlling the use of CCSS facilities to benefit private companies and researchers.
2010. The Supreme Court of Costa Rica stopped the implementation of clinical trials in humans until the necessary legislation was approved
2010-September 2013. Numerous bills regarding clinical research with humans introduced at the National Assembly were debated; none was approved. And the debate continues.

References

Acchío Tacsan, M. 2008. El desarrollo de los comités de ética e investigación en Costa Rica y su entorno nacional e internacional (The development of ethics and research committees in Costa Rica and national and international environment). *Revista de Reflexiones* 87(1): 73–85.

Arguedas, A. 2011. La necesidad de una ley en investigación clínica (The need of a law for clinical research). *La Nación*, 15 Feb. http://www.nacion.com/2011-02-15/Opinion/Foro/Opinion2684066.aspx. Accessed 1 Nov 2012.

Asamblea Legislativa. 1976. Proyecto de Ley de Reforma a varios artículos de la Ley General de Salud (Bill to reform several articles of the General Health Act). Expediente 7530. San José: Archives of the Legislative Assembly.

Asociación Costarricense de Bioética. 2004. Carta dirigida a la Dra. Zinia Cordero Vargas, Presidente del Consejo Nacional de Investigación en Salud (Letter to Dra Zinia Cordero Vargas, President of the National Health Research Council). ASCOBI 001.03. Mar 5.

Auditoría Interna de la CCSS. 1995. Informe sobre Evaluación del Convenio Caja Costarricense de Seguro Social/Instituto Costarricense de Investigaciones Clínicas para el Desarrollo de Proyectos de Investigación en el Área de la Salud AO-360-95 (Report on the evaluation of the agreement between CCSS and the Costa Rican Institute of Clinical Research for the development of health research projects).

Auditoría Interna de la CCSS. 2000. Evaluación del cumplimiento de la normativa institucional e internacional sobre la investigación en seres humanos en el los centros asistenciales de la Caja Costarricense de Seguro Social (Evaluation of compliance with institutional and international norms related to conducting research with humans in the clinics and hospitals of the CCSS). ACH125-R-2000. Área Auditoria Hospitales y Clínicas (Hospital and clinics' audit division). June 16.

Auditoría Interna de la CCSS. 2005. Análisis de eventuales incompatibilidades entre las funciones y el cargos desempeñado por la Dra. Olga Arguedas Arguedas en el ámbito de la investigación clica en seres humanos y como directora del CENDEISSS. AHC-220-R-2005. Área Auditoria Hospitales y Clínicas (Analysis of potential incompatibilities among the positions and functions of Dr Olga Arguedas Arguedas in the area of research involving humans and as director of CENDEISSS]. Área Auditoria Hospitales y Clínicas (Hospital and Clinics' Audit Division).

Cambronero Castro, J., M. Larios Ugalde, and W. Muñoz Céspedes. 2001a. La actividad clínica en los hospitales de la Caja Costarricense del Seguro Social y su impacto en los servicios y recursos de la institución (Clinical activity in the hospitals of the CCSS and its impact on the services and resources of the institution). In Asamblea Legislativa, Informe de Mayoría. Comisión especial que proceda a: Analizar la calidad de servicios, compra de servicios privados, utilización de recursos de la CCSS, para la enseñanza universitaria, medicamentos y pensiones (Legislative Assembly, Majority's Report. Special Commission to start analyzing the quality of the services, the purchase of private services, the utilization of CCSS resources for university teaching, pharmaceuticals and pensions). Expediente no. 13.980, 45–54. Apr 26.

Cambronero Castro, J., M. Larios Ugalde, W. Muñoz Céspedes. 2001b. La investigación utilizando seres humanos, en los servicios asistenciales de la CCSS (Clinical activity in the hospitals of the CCSS and its impact on the services and resources of the institution). In Asamblea Legislativa, Informe de Mayoría. Comisión especial que proceda a: Analizar la calidad de servicios, compra de servicios privados, utilización de recursos de la CCSS, para la enseñanza universitaria, medicamentos y pensiones (Legislative Assembly, Majority Report. Special Commission to start analyzing the quality of the services, the purchase of private services, the utilization of CCSS resources for university teaching, pharmaceuticals and pensions). Expediente no. 13.980, 55–65. Apr 26.

CCSS. 1998. Reglamento para la Investigación en los Servicios Asistenciales de la Caja Costarricense de Seguro Social. Aprobado por la Junta Directiva, artículo 17 de la sesión número 7211 de 24 de marzo de 1998 (Regulation of research to be conducted in clinics and hospitals of the CCSS. Approved by the Board of Directors, article 17 of the session number 7211. March 24, 1998). *La Gaceta* 91, May 13.

CCSS. Centro de Desarrollo Estratégico e Información en Salud y Seguridad Social. 2009. Principales hallazgos en el seguimiento de investigaciones (Main findings from monitoring investigations). *Boletín* 15: 6–7. http://www.cendeisss.sa.cr/etica/BOL-No15-2009.pdf. Accessed 1 Nov 2012.

Collado Martínez, H. 2010. Carta a la Dra. María Luisa Ávila Agüero. June 1.

De Young, K., and D. Nelson. 2000. Firms find Costa Rica 'special' place for trials; government struggles to keep up with drug testing. *The Washington Post*, 21 Dec 2000, p. 19A.

Merino del Río, J. 2006. Carta dirigida al Presidente de la República de Costa Rica, Oscar Arias Sánchez por un diputado de la Fracción del Partido del Frente Amplio (Letter to the President of the Republic of Costa Rica, Oscar Arias Sánchez signed by a Congressmen of the political party Fracción del Partido del Frente Amplio). JMR-JFFA-043-2006. May 12.

Fallas López, L.A. 2006. El péndulo maniqueo de la investigación clínica en Costa Rica (The Manichean pendulum of the clinical research in Costa Rica). *Diálogo (Costa Rica)* 7(1): 157–207. http://historia.fcs.ucr.ac.cr/articulos/2006/6Inves_clinica.pdf

Lakoff, A. 2006. High contacts: Gifts and surveillance in Argentina. In *Global pharmaceuticals. Ethics, markets, practices*, ed. A. Petryna, A. Lakoff, and A. Kleinman, 111–135. Durham: Duke University Press.

Mata, A. 2004. *Costa Rica ¿Edén de transnacionales en experimentacïón en seres humanos?* [Costa Rica, the Eden of transnationals for experimentation in humans?]. Semanario Universidad, p. 13. Dec 9.

Mininsterio de Salud. 1976. Veto. Comunicación del Presidente de la República Daniel Oduber y el Ministro de Salud Herman Weinstock (Communication of Daniel Oduber, President of the Republic, and Herman Weinstock, Minister of Health). San José: Presidential House. Dec 22.

Mohs, É. 2012. La investigación clínica. *La Nación* (Costa Rica). July 19.

Oconitrillo, T., and J. Fabio. 2002. La responsabilidad civil derivada de la investigación clínica en los servicios asistenciales de la Caja Costarricense del Seguro Social (Civil responsibility derived from clinical research in the health services of the CCSS). *Medicina Legal (Costa Rica)* 19(2): 93–102. http://www.scielo.sa.cr/scielo.php?pid=S1409-00152002000200011&script=sci_arttext. Accessed 1 Nov 2012.

República de Costa Rica. 1998. Reglamento para las Investigaciones en que Participan Seres Humanos. Decreto no 27349-S (Rules for research involving humans). *La Gaceta* 198. Oct 13.

Rodríguez, G. No date. ICIC: A model for clinical research in Latin America. Good practice in clinical research. Lecture 20. Segment 2. http://www.google.com/search?source=ig&hl=en&rlz=&q=ICIC%3A+A+model+for+clinical+research+in+Latin+America.+Good+practice+in+clinical+research.&btnG=Google+Search&aq=f&aqi=&aql=&oq=&gs_rfai. Accessed 1 Nov 2012.

Sala Constitucional. 2010. Carta dirigida al Sr. Hernán Collado Martínez (Letter to Mr. Hernán Collado). Tribunal Supremo de Justicia. Expediente no. 09-12222-0070-CO. Supreme Justice Tribunal. Record number 09-12222-0070-CO.

Subárea de Investigación y Bioética de CENDEISS. 2004. Carta del Coordinador de la Subárea de Investigación y Bioética del CENDEISSS al Director Ejecutivo del CENDEISSS (SAIB-230-08-04), p. 12. (Letter from the Coordinator of bioethics and research of CENDEISSS to the Executive Director of the CCSS). Sept 6.

Trejos, A. 1977. Las actividades del ICMRT en Costa Rica. Ejemplo de cómo los intereses comerciales pervierten la investigación científica (Activities of ICMRT in Costa Rica. Example of how commercial interests distort scientific research). Unpublished document.

Trejos, A. 1986. Semanario Universitario 754. Nov 28–Dec 4.

Chapter 9
Cervical Cancer and the Development of HPV Vaccines in Guanacaste, Costa Rica

Nuria Homedes and Antonio Ugalde

9.1 Introduction

Cervical cancer is the second most frequent cancer in women worldwide, and the second most frequent cause of cancer death for women between the ages of 14–45 years. Eighty-three percent of cervical cancer cases occur in residents of developing countries, and it is the primary cause of cancer deaths in women of Central America (WHO/ICO 2009). Unfortunately, cytology-based prevention programs (such as Pap smears) have been less effective in developing countries than in countries with adequate health systems (Robles and Roses Periago 2004), leading to continued efforts to develop better methods to prevent and treat the disease.

Between 1985 and 1987, the United States National Cancer Institute (NCI) sponsored a multi-center study to identify risk factors for cancer of the uterine cervix. The study group was composed of women living in the United States, Costa Rica, Mexico, Panama, and Colombia. The study resulted in one of the major health discoveries in the past two decades: that cervical cancer resulted from infection with the Human Papilloma Virus (HPV) (Herrero et al. 1997). The presence of the virus triggers a series of events that over the years can result in cancer.

Once the relationship between HPV infection and cancer had been recognized, hope arose that a vaccine to prevent infection and any resulting cancers could be developed. But not all women infected with HPV developed cancer, and it remained necessary to look for other contributors to the development of the disease. One such study, also sponsored by the NCI, took place in Guanacaste, Costa Rica, between 1993 and 2001. It is now known that the majority of HPV infections (more than 90 %)

N. Homedes (✉)
School of Public Health, Division of Management Policy and Community Health, University of Texas Houston Health Science Center, El Paso, TX, USA
e-mail: nhomedes@utep.edu

A. Ugalde
Department of Sociology, University of Texas, Austin, TX, USA
e-mail: augalde@mail.la.utexas.edu

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_9,

are self-limiting, but certain HPV serotypes (15 of the 40, which have been identified) may result in cancer of the cervix, vulva, vagina, anus, penis, or oropharynx if the infection persists (WHO/ICO 2009). Only two of these serotypes, 16 and 18, are responsible for 70 % of cervical cancers.

With this information, the NCI developed technology to prepare vaccines against HPV serotypes 16 and 18, and in 2004 and 2005 sponsored a Phase III trial with a vaccine produced by GlaxoSmithKline (GSK). This clinical trial took place in Costa Rica and recruited thousands of women, some of whom continued their participation in secondary studies on the effectiveness and safety of the vaccine.

Cervical cancer studies in Costa Rica are scientifically and probably economically important. An analysis of their implementation process reveals some of the administrative challenges and a series of conflicts of interest and ethical concerns faced by the sponsors of long term studies. This information has been obtained by groups of scientists, politicians, and journalists who have great knowledge of their country and also of the ethical principles that should guide research involving humans. They used different means and agencies – including the Legislative Assembly of Costa Rica and the Comptroller General of the Republic – to denounce irregularities and obtain information, which is usually kept secret.

Box 9.1 describes all the studies on HPV and cervical cancer conducted in Guanacaste. Box 9.2 describes the institutions and Costa Rican companies that had important roles in the study process, as well as their formal or informal interrelationships during the studies.

Box 9.1: HPV and Cervical Cancer Studies Conducted in Guanacaste

1985–1987. **Multi-center case-controlled study (United States, Costa Rica, Colombia, Mexico, and Panama) to determine the risk factors for cancer of the uterine cervix.** Sponsored by the United States National Cancer Institute (NCI). Conclusion: infection by certain types of human papilloma virus resulted in a series of events leading to cervical cancer.

1993–2001. **Study of the natural history of infection by the human papilloma virus in Guanacaste (Costa Rica).** Sponsored by NCI (N01CP-21081; N01CP-31061; N01CP 40542; N01CP 50535; N01CP 81023; NCT00342173). The goal of the study was to investigate why a small proportion of women infected with HPV developed cancer, but the majority did not; a secondary objective was to develop better techniques to detect cervical lesions. A future study would test a vaccine against HPV. One fifth of adult women (18 years or older) in Guanacaste were invited to participate in the study, plus all residents who developed invasive cervical cancer detected between June 1993 and November 1994 (n = 28) were included. The final sample was 10,049. A subsample of approximately 3,000 women was examined every 12 or six months to monitor the course of the disease. At the conclusion of the study, all women had a follow-up appointment.

2001–2003. Five studies took place utilizing various women in the cohort.

(continued)

Box 9.1: (continued)

2004. **A randomized, double-blind, population study of the efficacy and safety of a vaccine against HPV 16 and 18 developed by the NIH of the United States and produced by GSK** (NCI-04-C-N191, NCI-590299/009, GSK-590299/009, NCT00128661). This study took place in Guanacaste, Puntarenas, and Upala. From a total of 24,467 women, 7,466 were included in the study. Criteria were healthy women, from 18 to 25 years of age, not pregnant or breastfeeding, at least three months postpartum, and willing to use contraception from one month before the first vaccine dose until two months after the third. The follow-up period was for four years.

2009. Continued follow-up of healthy young women in Costa Rica, vaccinated or not vaccinated against HPV. Women vaccinated during the clinical trial received an additional six year follow-up, and 3,000 women were recruited to serve as an unvaccinated control group during the follow-up study period.

Box 9.2: Who Is Who in the Guanacaste Project

Costa Rican Social Security Agency (CCSS). A public agency responsible for the provision of health services to the population of Costa Rica. There is a regulation for the conduct of clinical trials (versions 1998, 2001, 2003, 2004, and 2005). Rules in 1998 and 2001 require contracts to be signed between the study sponsor and the Director of the center where the study will take place; in the 2003 and 2004 versions the contract is between CENDEISSS and the sponsor; changing again in 2005 to the sponsor and the Chief Medical Officer of CCSS (León González and Vargas Navarro 2006:258). All versions indicate that they should buy an insurance policy for each of the participants. The CCSS had a Committee for Ethics in Science (CEC), which became the Institutional Committee for Ethics in Science (CECI) in 2003.

Center for Strategic Development and Information on Health and Social Security (CENDEISSS). This Center is part of the CCSS and includes a Bioethics Unit, which, among other functions, has the responsibility to protect, regulate, advise, monitor, and manage studies with human subjects that take place in the health centers of the CCSS. It serves also as the technical office of COIBI-CCSS (Institutional Committee for Bioethics in Research)

Ministry of Health (MS). In 1998, when Dr. Rogelio Pardo was the Minister of Health, the Executive Decree 27349-8 for the conduct of clinical trials was issued. This Decree was in violation of CCSS regulations, and was challenged by the Legal Department and the Bioethics Unit of the CCSS. It was

(continued)

Box 9.2: (continued)

subsequently condemned by the Legislature for procedural irregularities and for having been prepared by people with conflicts of interest. In 1999, the Ombudsman's Office recommended the rejection or modification of the Decree, but it was not repealed until 2003 by Decree MS 31078-S (León González and Vargas Navarro 2006:243). In 2010, the Decree of 2003 (MS 31078-S) was itself repealed.

Costa Rican Institute of Research and Education on Nutrition and Health (INCIENSA). A State Institute attached to the Office of the Minister of Health, with responsibility for research in public health among other duties. The INCIENSA Ethics Committee approved the clinical trial conducted by PEG on May 28, 2004. This decision was later questioned by CONIS.

National Council on Health Research (CONIS). Founded by Decree MS 31078-S, it is an advisory and consultative Council to the Minister of Health on research involving human subjects. CONIS accredits ethics committees and research-conducting institutions, and registers and approves all research projects involving human subjects which take place in the country. It is financed by quotas on approved projects (5.5 %) (León González and Vargas Navarro 2006:244).

Epidemiology Project of Guanacaste (PEG). A private company with its own researchers which has been responsible for conducting studies related to the human papilloma virus and cervical cancer in Costa Rica. In August 2010, it had about 120 employees.

Costa Rican Foundation for Teaching in Health Sciences (FUCODOCSA). A private foundation attached to CENDEISSS, it was responsible for the financial management of clinical trials, and charged 15 % of the total budget.

INCIENSA Foundation (FUNIN). A private foundation established by the staff of the Costa Rica Institute for Research and Teaching Nutrition and Health (INCIENSA – Instituto Costarricense de Investigación y Enseñanza en Nutrición y Salud), an Institute of the Ministry of Health to administer PEG project funds, and can also channel funds from other health research projects. Its office is located in PEG. FUNIN works through the INCIENSA Ethics Committee for project approval. INCIENSA and FUNIN are closely related; for example, the Executive Director of INCIENSA was also Secretary of the Board of Directors of FUNIN, and the coordinator of INCIENSA's Ethics Committee was a member of the Board of Directors of FUNIN until April 24, 2004.

The University of Costa Rica. The University of Costa Rica is a public university, which has conducted laboratory tests for PEG since 1999, enabling it to purchase equipment valued at US $269,000.00.

9.2 Description of Guanacaste

Guanacaste is one of the seven provinces of Costa Rica. It is situated in the far northwest region of the country, with an area of 12,241 km^2 (7,606 sq. miles – almost one quarter of the country), and had 280,488 inhabitants in the year 2010 (about 6 % of the national population). Nicoya and Liberia are the two largest cities, with the remaining population dispersed in rural areas. The principal sources of income are cattle ranching and agriculture (with sugar cane and cotton being the major crops), with tourism developing during the past 10 years, especially along the 1,022 km (635 miles) of coastline. This change has reduced the poverty index in the province from 52 % in 1991 to 26 % in 2008.

As mentioned in the previous chapter, the Costa Rican Social Security Institute (CCSS) is the primary health services provider in Costa Rica, with almost universal coverage. It offers a broad package of good quality interventions and medicines, all of them free at point of service. The Ministry of Health is responsible for stewardship and public health activities, including community health and health promotion, especially in rural areas.

Guanacaste has always had one of the highest cervical cancer rates in Costa Rica, and in Latin America, averaging 33 cases per 100,000, age-standardized rate to the world population between 1982 and 1992, which is four to five times greater than the United States average (Herrero et al. 1997). This explains the interest of both the Costa Rican government and scientists, in studying this health problem in this population. Guanacaste, even with its low population density, has good health infrastructure: two regional hospitals, 11 health centers of medium complexity, and almost 100 health posts. All health posts have a health promoter who makes frequent health promotion visits to homes located in the service area, and all the facilities have electricity, a consulting office, and a waiting room. Herrero et al. (1997) reported that these centers were used only sporadically, and were ideal for epidemiological studies.

9.3 Epidemiological Studies on the Natural History of Cervical Cancer

A cohort study was begun in 1993 to (1) determine the role of HPV and other factors in the development and evolution of cervical cancer in residents of Guanacaste province; and (2) to study different laboratory techniques for the diagnosis of cervical lesions. Following the first survey and data analysis, follow-up studies of some of the women in the cohort were added, and a study of the effectiveness of a vaccine against HPV was announced.

The studies (N01CP-21081; N01CP-31061; N01CP 40542; N01CP 50535; N01CP 81023; NCT00342173) were conducted by a private company, the Epidemiology Project of Guanacaste (PEG) which in August 2010 had 120 employees, and were sponsored by the National Cancer Institute of the United States (NCI). The NCI

contracted the financial administration of the project to the Costa Rican Foundation for Teaching in the Health Sciences (FUCODOCSA), a private company, and also had collaboration agreements with the Ministry of Health (MS) for the use of the health infrastructure and with the Pan American Health Organization (PAHO) to facilitate tax-exempt importation of equipment and supplies (Herrero et al. 1997). Utilization of the CCSS infrastructure resulted from an agreement signed by the Executive President of CCSS and FUCODOCSA, which was never officially recognized by the Board of Directors of CCSS, and which expired in 1997. The reason why the agreement was never recognized by the CCSS is not known, but it is possible that it was due to a conflict of interest as the President of FUCODOCSA was, at the same time, director of the Center for Strategic Development and Information on Health and Social Security (CENDEISSS), a department of the CCSS.[1]

The central office of PEG was in San José, the capital of Costa Rica, and a field office was opened in each of the regional hospitals of Guanacaste (in Liberia and Nicoya). All vehicles and offices used during the studies carried the CCSS logo, and the study also utilized the CCSS radio (Herrero et al. 1997).

Between February and March, 1993, 95 health promoters from the Ministry of Health were trained to identify women over 17 years of age residing in a randomly selected geographic area where they expected to recruit 10,000 women. All the eligible women were invited to participate by means of a personalized letter, which included an appointment at the nearest clinic. If the appointment was not kept, home visits were made – sometimes by the health promoters of the Ministry of Health – to answer questions and offer transportation to the clinics. The study also included 28 residents of Guanacaste who, between June, 1993 and November, 1994, were being treated for cervical cancer at other hospitals. By December 1994, 10,049 women had been recruited (93.6 % of all eligible women) (Herrero et al. 1997).

During the first visit, women answered a questionnaire and gave a 15 ml. blood sample. Sexually active women received a pelvic examination, a cervigram,[2] and a test of the cells of the uterine cervix. Depending on the results, some women were referred for colposcopy in one of the two regional hospitals, together with randomly selected 2 % of the study participants. On referral, they answered a more extensive questionnaire, had additional blood and cervical cell tests, and biopsies when indicated. All the biological samples and the cervigrams were subsequently evaluated in various laboratories in the United States, and women diagnosed with serious lesions or with cancer received treatment through the CCSS.

Women who did not need cancer treatment were included in the cohort study, divided into groups by risk for developing cancer. Women at the greatest risk for developing cancer had follow-up appointments every six months (n = 492). Women with lower risk factors received annual follow-ups (n = 2,574), and the remainder (n = 6,034) had a passive follow-up, every five to seven years, with instructions to keep appointments for routine examinations at the CCSS. Each follow-up visit

[1] According to information presented in the Asamblea Legislativa de la República de Costa Rica (2005) he was also the principal investigator for PEG.

[2] Photographic images of the cervix

included a repetition of tests performed at the first visit, and a questionnaire on behavioral changes. All women with possibly serious lesions were referred for colposcopy and medical treatment, and were withdrawn from the study. After seven years, all the women remaining in the study were re-evaluated, but 14.9 % of women in the passive follow-up group could not be located (Bratti et al. 2004).

This is the largest cohort study worldwide for HPV and cervical cancer, and had good quality control. The richness of information gained from this study has resulted in many scientific publications and has maintained interest in studying this population. Between 2001 and 2003, other studies took place with many women from the cohort, to (1) determine HPV genetic factors associated with grade three intra-epithelial neoplasms and cervical cancer; (2) provide follow-up to women with high grade cytological lesions or cervical cancer; (3) observe differences in fluctuations in immunological markers during the menstrual cycles between women using or not using contraceptives; (4) study the indicators of HPV infection in women between the ages of 45 and 70 years; and (5) analyze the immunological indicators of the natural history of infection with cancer-causing HPV (Proyecto Guanacaste n.d.).

This knowledge has been of crucial importance in the development of vaccines to prevent cervical cancer. It has also, however, given rise to major controversy in the country.

9.4 Questions Related to the PEG Company, the Dismissal of FUCODOCSA, and the Change to FUNIN

Although the year the project began is officially considered to be 1993, 1991 dated documents requesting CCSS guidance on appropriate techniques for the transportation of biological specimens indicate that some project activities had already commenced.[3] For its part, the CCSS Ethics Committee never approved the project, although one publication (Herrero et al. 2000) stated that the project had been approved in Costa Rica by an institutional ethics committee. Other publications (Herrero et al. 1997; Bratti et al. 2004) do not include statements of approval by an ethics committee.[4]

PEG projects were not alone in being questioned. At the end of the 1990s there were many complaints about irregularities in the conduct of clinical trials in sessions of the Legislative Assembly. On October 11, 1999, the Board of Directors of the CCSS admitted irregularities, and asked for an investigation by the Internal Audit department. Eight months later, the audit report agreed with the complaints made to the Legislative Assembly and the Board of Directors.

[3] Personal communication, José Miguel Esquivel Chinchilla.

[4] Legislation in effect at that time in Costa Rica, Executive Order of December, 1975, required that a participant must consent to participate in research and that an Institutional Scientific Committee must be established to evaluate the ethical and scientific aspects of the study.

Referring to PEG, the Internal Audit of the CCSS (Auditoria Interna de la CCSS 2000) and other studies raised the following issues:

- Utilization of infrastructure, vehicles, equipment, supplies, and personnel from the public health services network without the knowledge of the CCSS, without compensating the public sector and leading study participants to identify the project as a governmental initiative, a factor that could have influenced their decision to participate
- Non-compliance with the CCSS regulations. The unofficial agreement between the Executive Director of CCSS and FUCODOCSA for the PEG project expired in 1997, yet the project continued. The CCSS never approved the implementation of the project, which was not evaluated by its Ethics Committee. CCSS was not able to review the informed consent form
- Contracts for the study to take place in CCSS facilities were established through intermediaries, in this case FUCODOCSA, which benefitted economically, although many personnel were CCSS employees and received a salary from CCSS for serving this population. FUCODOCSA received 15 % of the contracts they administered, which amounted to 1 million dollars during the first five years of the PEG project (Asamblea Legislativa de la República de Costa Rica Legislative Assembly 2001:60[5])
- Contracts and agreements including the use of public resources by private companies were in violation of Article 11 of the Political Constitution and Article 11 of the General Law of Public Administration. This was confirmed during a meeting in 1997 (León González and Vargas Navarro 2006:108)
- Possible violation of Law 6577, which prohibits the use of CCSS facilities and equipment for private medical practice such as the use of hospitals and clinics for clinical trials (León González and Vargas Navarro 2006:109)
- Accusations that the Medical Directors of CCSS and CENDEISSS did not comply with the policies of the CCSS Board, and had acted outside the law

In addition, the CCSS audit (Auditoría Interna de la CCSS 2000) confirmed that the existing regulations in Costa Rica were not sufficient to protect study participants because, according to existing laws, the sponsors and clinical researchers were not punishable. As mentioned in Chap. 8, new bills have been proposed, but up to this date (November 2013) none has been approved. This may explain the behavior of those involved in carrying out clinical trials, including those responsible for their oversight (León González and Vargas Navarro 2006:273; Castro Fernández 2002).

The majority report of the Legislative Assembly (Asamblea Legislativa de la República de Costa Rica 2001) arrived at similar conclusions[6] and using various

[5] This Majority Report was prepared by two members of the Partido de Liberación Nacional and one of Partido de Integración Nacional

[6] Criticized that most of the clinical study was designed by external investigators and implemented through private companies acting outside the rules of the CCSS and international standards (Asamblea Legislativa de la República de Costa Rica 2001:58–59)

reports of the CCSS Internal Audit (AO-360-95; AHC-300-R-98; AHC-125-R-2000) exposed conflicts of interest and administrative actions which left study participants unprotected. These reports involved high executives at CCSS, including the Board of Directors (see Box 9.3). The reports indicated that the greatest contribution to the weakness of the system was complicity between the Executive President and the Medical Director of CCSS, CENDEISSS, and the physicians who have dual employment, that is, they work for CCSS while at the same time own companies that facilitate the implementation of clinical trials in the country. For example, the Medical Directors of CCSS and of CENDEISSS participated in writing the Ministry of Health Decree of 1998, which contradicted the standards of CCSS, authorized clinical trials that did not comply with CCSS standards, and eliminated the systems of control and follow-up of clinical trials. At the same time, the Medical Director dissolved the CCSS Bioethics Committee, which had functioned adequately, and replaced it with another consisting of participant recruiters, the assistant director of CENDEISSS (who was the Principal Investigator in clinical trials carried out in the CCSS hospital San Juan de Dios), clinical trial researchers, and the manager of FUCODOCSA. The majority report recommended an investigation on experimentation with human subjects and the immediate re-instatement of the CCSS Ethics Committee.

Box 9.3: Conflicts of Interest

The relationship of FUCODOCSA – CCSS

On March 26, 1992, the President of CCSS signed an agreement with the owner of a company for clinical research, (ICIC.SA) to conduct studies involving human subjects in the CCSS facilities for 10 years. During negotiations, CCSS was represented by the Director of CENDEISSS, who was also President of FUCODOCSA and supervisor of the owner of ICIC, who was also working at CCSS. The agreement was signed without being reviewed by the Legal Office of CCSS, and was approved by the CCSS Board of Directors eight days later. This agreement was never monitored nor controlled by the CCSS (Legislative Assembly. Majority's report 2001:60; Bloque Patriótico Parlamentario 2004).

In January, 1993, the President of CCSS signed a five-year agreement with FUCODOCSA to carry out the PEG program. The principal participants were the same as in the 1992 agreement, and the President of FUCODOCSA continued as Director of CENDEISSS. This agreement expired in January, 1997, and was not renewed.

The relationship of CCSS – CENDEISSS

There was a conflict of interest between the Medical Directors of CCSS and CENDEISSS. In 1998, the Medical Director of CCSS nominated the Director and Assistant Director of CENDEISSS, who, without legal support, decided

(continued)

Box 9.3: (continued)

not to apply the standards of CCSS. The Assistant Director of CENDEISSS conducted clinical trials at the CCSS hospital San Juan de Dios (Legislative Assembly. Majority's report 2001).

The relationship between the Ministry of Health – INCIENSA, and FUNIN
The project was presented to the public as if FUNIN would strengthen the programs of INCIENSA, even though INCIENSA's mandate does not include the implementation of pharmaceutical research. FUNIN's employees were working for INCIENSA. INCIENSA did not receive financial compensation.

The relationship between CEC-INCIENSA-FUNIN
In May, 2004, the Coordinator of the Ethics Committee of INCIENSA, approved the research protocol for the study carried out by the PEG company in Guanacaste. Before accepting the Coordinator position, she had been employed by FUNIN.

Other conflicts of interest
In January, 2004, Dr. Olga Arguedas joined PEG, but left in August, 2004 to become the Director of CENDEISSS (without competition). Dr. Olga Arguedas was a member of the Ethics Committee of the Children's Hospital, where the Minister of Health during the two most recent governments (2006–2010, and 2010–2011) –did much of her research (Mora Ramírez 2006a). (see also Chap. 8)

Private companies conducting clinical trials often hired former or current CCSS employees.

These conflicts of interest, in addition to enriching the private sector at the expense of the public, left the study participants unprotected, and increased the difficulty of obtaining information. Not even the Internal Audit Department of the CCSS could gain access to the informed consent procedures of many projects (León González and Vargas Navarro 2006), and the PEG company systematically refused to provide information to the Internal Audit Department and the Board of Directors of the CCSS (Asamblea Legislativa de la República de Costa Rica 2001:61).

The Comptroller General of the Republic also conducted fiscal studies and repeatedly called to the attention of the CCSS executives their neglect in resolving the problems shown in the 2000 CCSS audit and their slowness in implementing the recommendations called for in the CCSS audit, in other reports written by the Legislative Assembly, by the CCSS Board of Directors, and by the Comptroller's office (Masís Figueroa 2003).

The CCSS audit (Auditoría Interna de la CCSS 2001) recommended that the contract with FUCODOCSA to test the efficacy of the HPV 16/18 vaccine not be renewed until: (1) all the problems identified in various audits and reports were

corrected; (2) mechanisms were established to protect study participants; (3) CCSS executives with conflicts of interest were not permitted to have input into the project, and (4) it was determined if an agreement for vaccine studies could be made directly with the NCI, USA.

In January, 2004, the Principal Investigator of the PEG company wanted a contract between FUCODOCSA and the medical administration of CCSS to conduct colposcopy studies on CCSS patients in PEG clinics, stating that CCSS did not have sufficient equipment available. The auditing department analyzed the contract and recommended that it not be signed, among other reasons, because (Asamblea Legislativa de la República de Costa Rica 2005:15–18[7]):

> . . . once more, an attempt is made to involve the institution in research with human subjects without clearly establishing and properly defining responsibilities in the relationship, which eventually could have legal implications because it would support an activity sponsored by a private company

As a result, FUCODOCSA resigned from its association with PEG.

The Minister of Health, Dr. María Rocío Sáenz, tried to rescue the project and proposed to the NCI that the INCIENSA Foundation (FUNIN)[8] be contracted (Asamblea Legislativa de la República de Costa Rica 2005:26–27) arguing that:

> . . . [FUNIN is] linked to the health sector because it operates in support of the Costa Rican Institute of Research and Education on Nutrition and Health (INCIENSA), an organization attached to the Ministry of Health, and could take over the financial administration of the project

She added that the Ethics Committee of INCIENSA had approved the protocol, was committed to the project, and had signed a letter of intent with NCI. On April 30, 2004, the recently created FUNIN assumed all the rights and obligations associated with the clinical trial of the safety and effectiveness of the GSK vaccine HPV 16/18 (see Box 9.3.)

9.5 The Second Part of the Project: Safety and Efficacy of the HPV 16/18 Vaccine

The Phase III clinical trial to test the safety and efficacy of the HPV 16/18 vaccine was a double blind, randomized study to be conducted over eight years (NCI-04-C-N191, NCI-590299/009, GSK-590299/009, NCT00128661). It was funded by the NCI, which contracted with FUNIN to act as intermediary. PEG, which now had its own facilities, continued to be responsible for carrying out the study, and, although

[7] This Unamimous Report was prepared by members of the following political parties: Partido de Liberación Nacional, Bloque Patriótico, Partido Unidad Social Cristiana, Partido Patria Primero and Partido Movimiento Libertario

[8] Communication DM-1759-04, Dr. Sharon Miller, contracts officer for NCI research contracts. Cited in Asamblea Legislativa de la República de Costa Rica (2005)

there was resistance from CCSS, patients found in need of medical treatment were referred to CCSS clinics. GSK provided the experimental vaccine. From 24,467 healthy women between 18 and 25 years of age, a total sample of 7,466 was selected to participate in the study. Of this number, 3,727 received the HPV vaccine, and 3,739 received the vaccine for Hepatitis A. Study participants had to agree to use any method of contraception (including withdrawal or abstinence) beginning one month before receiving the vaccine until two months after the third dose; they could not be breast-feeding, and they had to be at least three months post-partum. Study details and procedures the women would undergo were included in a table at the end of the informed consent.

The project was valued at almost US $20 million, and FUNIN probably received about US $3 million for its administration. Implementation of this study had the ethical-administrative problems discussed below (see Box 9.4).

Box 9.4: Organization and Ethical Problems of the Clinical Trial of the HPV 16/18 Vaccine (NCI-04-C-N191, NCI-590299/009, GSK-590299/009, NCT00128661)

Study responsibility: Epidemiological Project of Guanacaste (PEG)

Contract between NCI – FUNIN (INCIENSA Foundation). Signed April 30, 2004.

Approved by the ethical committees of INCIENSA, the University of Costa Rica, and CONIS.

Use of the same public resources used during the study of the natural history of cervical cancer (including physical infrastructure, vehicle, radio system and personnel). PEG clinics were also used.

The Ministry of Health promised to obtain the assistance and approval of CCSS, but never did.

Administrative and ethical problems

In 2005, a Legislative Commission censured the Minister of Health at that time, Dr. María del Rocío Sáenz, for ethical, legal, and administrative problems with projects that she directed (Mora Ramírez 2006b).

CONIS reprimanded the INCIENSA ethics committee for approving a project which did not meet existing standards.

Recruitment of study subjects began before receiving the approval from CONIS and the ethics committee of the University of Costa Rica.

CCSS wanted to separate from PEG, but was not able to. Its name was included in the informed consent material.

The contract between the NCI and FUNIN stated that explicit support and approval had to be obtained from the Ministry of Health and from the CCSS, as well as from all the ethics committees, for the expected eight years of the duration of the study. CCSS never reviewed nor authorized the project.

(continued)

Box 9.4: (continued)

The sponsor did not cover the cost of adverse reactions. The consent form stated that women in any way involved with the study could receive treatment from the Ministry of Health or CCSS if they had any adverse effects.

CCSS infrastructure was used, with the excuse that physicians were involved in the "Mixed Medicine" program.

Employees of a private project had access to CCSS patient files, but no note was made in the clinical history of the CSSS stating that the woman was taking part in a research study.

More than one million biological specimens were sent outside the country without any formal agreement.

According to the NCI – GSK contract, all the intellectual property rights were retained by NCI and GSK, and they were governed by US law.

It was not determined how the study results would benefit Costa Rica and its citizens.

Some participating women did not understand the informed consent material.

9.5.1 Relation with CCSS

The relationship between PEG – FUNIN – CCSS was controversial. CCSS did not want to be part of the trial conducted by PEG, yet the CCSS name continued to appear on project documents. This was questioned by the institutional ethics committee (CECI) and the CCSS auditor, neither of whom had reviewed nor approved the project (Asamblea Legislativa de la República de Costa Rica 2005:18–19).

In December, 2004, in a meeting between three representatives from PEG, the President of the CECI, the Director of CENDEISSS, and the Executive President of CCSS, it was decided not to remove the name of CCSS from the informed consent, and to maintain the message that if the women in the study had any medical problem they should seek treatment through the CCSS. A note was added clarifying that the CCSS was not part of the research team for the clinical trial. This indicates that the CCSS executives ignored the concerns expressed by the CCSS compliance offices (Asamblea Legislativa de la República de Costa Rica 2005:19).

In January and February 2005, the Comptroller General of the Republic and the Executive President of CCSS, reversing the December, 2004 position, said that the CCSS name should not appear anywhere, because CCSS had not agreed to be a part of the clinical trial, and that to continue to include the name or services of the CCSS in the official documents of a private project could result in a legal summons (Asamblea Legislativa de la República de Costa Rica 2005:20). The final version of the informed consent included a phrase stating that the CCSS was not part of the research team, which could give the impression that it was involved in other activities. The PEG non-compliance with the requirements of the Comptroller and CCSS has not had any consequences.

The CCSS position was a problem both for the Ministry of Health and for FUNIN. A year earlier, on December 12, 2003, while negotiations on how to

administer the project were ongoing, the Minister of Health signed a letter of intent with NCI confirming that the work of PEG was of interest to the Ministry of Health and of importance to the people of Costa Rica, and agreeing to facilitate the authorization of CCSS to implement the clinical trial of the vaccine and give access to health records (Asamblea Legislativa de la República de Costa Rica 2005:2). FUNIN, upon accepting the contract with the NCI, agreed to obtain the support and explicit approval of the CCSS and the Ministry of Health for the duration of the project[9] (Asamblea Legislativa de la República de Costa Rica 2005:21).

FUNIN, without obtaining institutional support, decided to enroll seven PEG physicians in the "mixed medicine" program[10] so that they could refer patients to the clinics and welfare services of CCSS, even though this program was not set up to include clinical trial participants. Standards for research conducted in CCSS facilities stated that all economic aspects related to clinical research had to be in a contract which included, among other items, 100 % reimbursement of incurred costs (Asamblea Legislativa de la República de Costa Rica 2005:21–22). By using the "mixed medicine" program, FUNIN: (1) improperly used the CCSS "mixed medicine" program because the PEG clinics had been set up to conduct research, not ambulatory care; (2) gave a false understanding that the CCSS was a part of the research project; (3) transferred project costs to the CCSS, which did not receive any financial compensation for the referred patients; (4) violated CCSS standards, and (5) facilitated private sector access to the clinical records of the CCSS,[11] with the additional violation that the participation of the woman in the research project was not recorded in her clinical record. Eventually, this last situation caused administrative action against FUNIN employees (Asamblea Legislativa de la República de Costa Rica 2005:28).

9.5.2 Problems with Approval by the Ethics Committee

Despite all these controversies and conflicts of interest, this research project was approved by three ethics committees – those of INCIENSA (May 30, 2004), the University of Costa Rica (December 1, 2004), and CONIS (November, 2004). Of the three, only CONIS questioned the approval of the clinical trial for not complying with existing standards. In September, 2004, CONIS wrote an official letter to a member of the INCIENSA ethics committee questioning the approval of the clinical trial, which, in CONIS opinion, had been granted with insufficient and

[9] Contract N01-CP-11005, signed on April 27, 2001, by Dr. León de Mezerville Cantillo and Dr. Sharon Miller (NCI), and amended on April 30, 2004, when FUCODOCSA resigned from its association with PEG, and FUNIN became responsible.

[10] The CCSS mixed medicine program (*programa de medicina mixta*) allows physicians in private practice, who enroll in the program, to refer CCSS beneficiaries, seen in their private practice, to CCSS facilities for medications and health services, including diagnostic tests and hospitalization.

[11] This violated Articles 12 and 16 of the General Law of Internal Control, No. 8292 (Asamblea Legislativa de la República de Costa Rica 2005:9).

incomplete information (a lack of insurance policies and copies of contracts, and problems with informed consent). Not receiving an adequate response, CONIS cautioned the ethics committee and the Director of INCIENSA that they should respond to their concerns. Finally, in November 2004, almost five months after the study had begun, and after 1,599 doses of the experimental vaccine had been given, CONIS stated that they had received the insurance policies and approved the project. CONIS approved the project knowing the conflicts of interest between the INCIENSA ethics committee and FUNIN. CONIS knew that the coordinator of the ethics committee had been a member of the Board of Directors of FUNIN until April 21, 2004. Surprisingly, CONIS announced that a letter of resignation from the Board of Directors of FUNIN was sufficient to indicate that there was no conflict of interest (Informe de Conis 2005).[12]

9.5.3 Donation of Materials for Research in Other Countries and Benefits for Costa Rica

The informed consent said that the specimens would be stored in a space sponsored by the United States National Institutes of Health, without specifying how they would be used and in violation of existing regulations. The contract with the NCI[13] stated that the collection of biological specimens had to comply with local standards, and Costa Rica requires the signature of transfer agreements protecting the intellectual property rights of the participants or the national institutions (Asamblea Legislativa de la República de Costa Rica 2005:37). These agreements were not established by the PEG Company, although a very large quantity – more than one million- biological specimens were exported. In contrast, clauses related to intellectual property and patents are highly detailed in the contract between NCI and GSK.

The informed consent did not mention how the results of the study would benefit participating women or the population of Costa Rica, and it was not until the middle of 2005 that this topic received attention.[14] Additionally, such was the interest that the study should take place in Costa Rica that, due to the intervention by CONIS, the PEG Company was exonerated from payment of 0.5 % of the project's total budget to the Ministry of Health (Vargas Carmona 2005).

[12] The delays in the signature of the contract between FUNIN and the University of the Costa Rica explain the delay in project approval by the University's IRB.

[13] N01-CP-11005 cited in (Asamblea Legislativa de la República de Costa Rica 2005)

[14] In contradiction to the principles behind Executive Decree No. 31078-S (Asamblea Legislativa de la República de Costa Rica 2005:39).

9.5.4 *Problems with Informed Consent and the Recruitment Process*

A report from the Board of Directors of the College of Physicians (Páez Montalbán 2005) questioned the imprecision of the informed consent process, demonstrated the presence of contradictions in the text (which could confuse participants and in some cases put them in danger), and warned that the presentation of the information and the various omissions of content could have altered the participants' response. For example, while one part of the document stated that the women had to use contraceptives, another section minimized the importance of pregnancy stating that there was no evidence that the vaccine endangered the pregnant woman or her fetus; the text implied that the vaccine would prevent HPV infection without mentioning that there was a high probability that they already had or had had the virus, and also that the project was of public interest when the greatest beneficiaries were institutions and private companies. Nowhere was it said that one of the study objectives was to monitor the occurrence of adverse events, including the appearance or exacerbation of auto-immune diseases, nor did it mention that the researchers wanted to study the effectiveness of the vaccine in women infected with HPV, and in pregnant women.

Without underestimating the importance of the above mentioned concerns, there were other problems with recruitment and the process of obtaining informed consent. The newspaper *Pregonera* (Town Crier) of Costa Rica published a special report (Vargas Carmona 2005) that included interviews with six women who were "invited" to receive the vaccine, providing insight into the recruitment process and the women's understanding of this clinical trial. In the following paragraphs we reproduce some excerpts of those interviews (our translation).

9.5.4.1 Marianela Alvarado Solano. "It is an Experiment."

Mariana Alvarado Solano lives in the "El Guabo" neighborhood. She is 24 years of age, and before going to work she had to leave her nine year old daughter in school and her three year old toddler in the care of her mother.

> We asked her "what was the first contact you had with the project?" She replied "a young man came with an invitation, and said that I was lucky to be in this project, that I would be like a guinea pig participating in it."
> Interviewer: Why like a guinea pig?
> Marianela: "Because it is a study, it is something experimental"
> Interviewer: This is what they said about the project?
> Mariamela: "Yes, and they gave a pamphlet which explained quite a bit, they told me that it was a blind study and that no-one would know the type of vaccine I would receive."
> This young mother had been vaccinated twice and stated: "I went mostly because my mother told me it was good because they were helping people and giving people physical exams"

9.5.4.2 Johanna Gutiérrez Gutiérrez. "Nobody Told Me Anything."

Johanna Gutiérrez Gutiérrez, is a young 23 years old woman who worked with her mother in a food stall. In addition to her work, she studied Family and Social Education. Johanna said that she did not want to be vaccinated, but a friendly young man came to her house and gave information about the project as well as an appointment. We asked her "*why did you not want the vaccine?*" In her own words:

> because from the beginning nobody explained anything, the pamphlet had some information, but the truth is that I did not feel it was safe, that is, there was too much I didn't know, and this is why I was afraid and when I talked to my friends that had already been vaccinated they said that they did not know what was in the first vaccine

Johanna had doubts, and said that she was not going to be among those vaccinated, questioning the focus of the project:

> just think that they want you to feel so special that they say 'we will pick you up and take you back' and the truth is that no one has seen this before and we want to know - What is the real interest of these people?

9.5.4.3 Alejandra Morales Álvarez. "Something Strange Happened to Me."

Behind the display case in the shop where she worked, we talked to Alejandra Morales Álvarez, the youngest of those interviewed. She had been told:

> that it [the study] was a test that was going to be done on women, emphasizing that it was a virus transferred through. . .well, when you were with a man

She told us that in the clinic she saw films and they asked her questions such as "how many men have you had relations with?", and then they gave her the vaccine. She said that after the vaccine she felt very ill and did not go to work –

> my arm was very red, I felt nauseated, but they (the people in the clinic) told me that this happened; in a few days I pressed my breasts and had a milky discharge, which is still there. I went to the doctor who examined me and I asked her why I had this after the injection and she said that it was too many hormones, but I still have it

Alejandra has had breast complications for 2 months, and assured *Pregonera* that she would not go to the clinic because in her opinion they did not know how to adequately help her.

9.5.4.4 Yanel Contreras Cavaría. "It is too Much."

Yanel is a 22 year old woman who lives in the Santa Cecilia neighborhood. A good part of her time is spent working as a receptionist in a beauty salon. She is on the list

of eligible women, but refused to participate. This resident of Guanacaste does not trust the regulations and the insistence of the project staff that she participates:

> they told me that they would fetch me if I could not go, that I would only have to call. They gave me an appointment, and if I couldn't keep it, they would change it, I could go to the clinic when and as often as I wanted; I live 300 meters (just over 300 yards) from the clinic, and that they would send a big car to pick me up, this is too much

Yanel has not been vaccinated, and took that decision because of the project conditions such as avoiding a pregnancy, as well as hesitation about the safety of the series of examinations to which she would be exposed.

On the other hand, she had several questions. One is that she knows that the CCSS does not participate in PEG; but

> they (the project people) say that CCSS agrees with the project, and they gave me the example of the many doctors who are working with them

9.5.4.5 Querely Araya Morales. "I Decided to Be Vaccinated"

Querely Araya Morales is included in the list of women who have been vaccinated. Born in Santa Cruz, Costa Rica, she is the single mother of a three year old daughter. At 22 years of age, she is employed by a local store. She has received two dosages of the vaccine, and, as with the other women, we asked her about the information she was given prior to agreeing to take part in the PEG study:

> the young woman explained to me that the vaccine had no problems; that more than one thousand women in Liberia had been vaccinated, and that there were two types of vaccine, for "papilloma" and the other, I think, for hepatitis, but they could not tell us which we would receive because it is decided by chance." Following this explanation, I decided to be vaccinated because" it sounded good to me, the young woman said that it was to prevent cancer from HPV and this seemed a good idea

Asked about the effects after receiving the vaccine, she said

> my body was itching and two days after being vaccinated I had a menstrual period which lasted almost 10 days, and my periods are still irregular

At the end of our conversation, Querely stated that she had decided to continue with the remaining vaccinations because for her "everything was fine."

9.5.4.6 Jenny Rodríguez Gómez. "Women Must Be Warned."

At 24 years of age, with two children to care for and her job, Jenny Rodríguez Gómez is dedicated to "warning" the women of Guanacaste through various articles in the *El Sabanero* newspaper. This young woman did not participate in the study because, she said, she really studied the project.

> I read all that they gave me and I had doubts; I talked to some local physicians and they told me that receiving the vaccine or not was my personal decision, but it wasn't recommended because of bad reactions

Having made the decision not to be vaccinated, she wanted to share her point of view with other women by publishing several articles, which, in her words, "have become the foundation of the Congressman's reports." She added:

> "it seems to me that they are offering too many things; that made me suspicious, and I wanted to alert other women. . .because here we are known for being very meek people." Jenny emphasized the importance of being well informed, and "invited women to study this project, not to sign the consent without reading it, to ask for a copy, and that if they had a friend who knew the law, that they talked to that person"

This clinical trial has greatly contributed to the advancement of knowledge on the epidemiology and prevention of cervical cancer, and has also allowed many scientists – including Costa Ricans – to publish articles in prestigious scientific journals. In the words of the President of the University of Costa Rica:

> The University has been enriched by this scientific investigation, becoming an institution in the forefront of this topic worldwide

The studies in Guanacaste continue (see Box 9.1), and it is very probable that they will contribute to scientific knowledge. It is not known if, in the process, ethical-administrative irregularities will also continue, and if the advances in knowledge will benefit the women who participated in the study and the Costa Rican population in general. At present the vaccine is very expensive for national economies such as that of Costa Rica, which prevents the public health sector from offering it to all adolescents.

9.6 Conclusions

Costa Rica has a long tradition of clinical research, and complaints about irregularities in research involving humans date from the mid-1970s. These irregularities have been attributed, at least partly, to the absence of an appropriate legislative framework, but the complicities documented in this article question if a new law will resolve the problem. Public agencies and the judicial system are responsible for ensuring compliance with existing laws and regulations but, as this case study illustrates, individual agendas of powerful researchers and conflicts of interest among senior executives of public institutions (CCSS and the Ministry of Health) can derail all efforts, including those of the Legislative Assembly, to remedy the situation.

The problems described in this chapter are not due to ignorance or lack of information. In this case study, the PEG company, the researchers, the intermediaries (FUCODOCSA, FUNIN), the public institutions (CCSS, Ministry of Health, INCIENSA), the legislators, and the agencies responsible for respecting the rights of research participants (CONIS, CENDEISSS, CEC-INCIENSA) were aware of the irregularities that affected the PEG projects. For example, the same person that as Minister of Health promoted in 2003 and 2004 the activation of the clinical trial

through FUNIN a year earlier (August, 2002) had stated (Asamblea Legislativa de la República de Costa Rica 2005:8):

> Research benefits are not helping the public institutions where the research takes place, the institutions do not benefit either economically or from the results of the studies, although the studies take place in the facilities of these institutions. . . There is no clear separation of duties between those who authorize the studies and those who take part in the research. . . At present, clinical studies are rapidly moving to the private sector. . .

The stories of the women of Guanacaste show that they were of humble origin, were not informed sufficiently about the study, and some had felt coerced by recruiters. We do not know how this influenced the quality of information obtained in the study, for example: were all perceived adverse events shared with the PEG physicians, or, as in the case of Alejandra, did women leave the study without further explanation? Or, as with Querely, they failed to report the effects of the vaccine because they were not thought to be very important? How many of these women experienced other complications that could not be linked to the vaccine, because they received treatment from CCSS without informing the PEG company physicians and without the CCSS physician knowing that the woman was a participant in the study?

Study sponsors are often aware of these problems and conveniently choose to ignore them. For example, the contract with NCI failed to address intellectual property rights issues, did not specify the benefits for the Costa Rican population and did not require the insurance policies for research participants. NCI knew the problems between FUCODOCSA and the CCSS, but had no problem transferring the contract to another private body, FUNIN, without modifying the terms of the contract, as they would have had to do in high-income countries. Moreover, if the NCI and GSK had monitored the implementation of this clinical trial, they would not have been able to overlook the concerns about the project voiced by the CCSS Auditor, the Comptroller General of the Republic, and the Legislative Assembly. The possibility that the NCI and GSK preferred to ignore those problems, many of which had simple solutions, and obtain the data at any cost, marks them as accomplices.

Also of note is that Costa Rica has not required sponsors to pay custom duties for the importation of supplies and equipment, or for the use of facilities, supplies, equipment, and personnel. No one knows the amount of the debt, but if it is not collected and this issue is not addressed in future contracts, Costa Rica will continue to subsidize foreign sponsors and the pharmaceutical industry in exchange for very few benefits. As in this case study, the Costa Rican population pays for some research expenses that are not reimbursed to the CCSS, and the main benefactors from clinical research are the Costa Rican researchers, academics, and intermediary agencies – in this case, FUCODOCSA and FUNIN-, and the pharmaceutical companies.

The problems described in this chapter can only be resolved by the express commitment of study sponsors, who have in their power not only the ability to establish standards of good clinical practice, but also compliance with ethical principles and national and international standards governing research involving humans. Regulatory agencies in high-income countries must also question the quality of information obtained in countries which do not uphold these principles.

At the same time, consumer advocacy groups and organized community representatives should establish and maintain pathways to channel information and complaints related to the conduct of clinical trials.

Acknowledgment We thank José Miguel Esquivel, Hernán Collado, Rafaela Sierra, Carlos Agustín Páez, and Carlos Zamora for sharing documents and information about this project, and for their critiques of earlier versions of this article. The authors remain responsible for the analysis of the data and the conclusions of this chapter

References

Asamblea Legislativa de la República de Costa Rica. 2001. Informe de Mayoría. Comisión especial que proceda a: analizar la calidad de los servicios, compra de servicios privados, utilización de recursos de la CCSS, para la enseñanza universitaria privada, medicamentos y pensiones. Expediente No 13.980. Prepared by Cambronero J, Castro, Larios Ugalde M, Muñoz Céspedes W (Majority's report. Special commission to start: analyzing the quality of services, the purchase of private services, and the utilization of CCSS resources for university training, pharmaceuticals and pensions).

Asamblea Legislativa de la República de Costa Rica. 2005. Informe Unánime. Experimentación en seres humanos en Costa Rica y el Proyecto Epidemiológico Guanacaste. Comisión especial investigadora para el estudio y seguimiento de los programas sociales y las políticas de salud. Expediente No 14.948. Prepared by de la Rosa Alvarado K, Rodríguez Mena P, Jiménez Madrigal Q, et al. (Unanimous Report. Human experimentation in Costa Rica and the Epidemiological Project Guanacaste. Special research commission to study and follow-up social programs and health policies).

Auditoría Interna de la CCSS. 2000. Evaluación del cumplimiento de la normativa institucional e internacional sobre la investigación de seres humanos en los centros asistenciales de la Caja Costarricense de Seguro Social. AHC-125-R-2000. (Evaluation of compliance with institutional and international norms for research with humans in the clinics and hospitals of the CCSS).

Auditoria Interna del CCSS. 2001. Informe de Auditoría (Audit Report) AHC-104-A-2001, June 5.

Bloque Patriótico Parlamentario – Office of Humberto Arce, National Legislative Assembly. 2004. Pacheco denied irregularities at CCSS (Pacheco negó irregularidades en la CCSS). *Cyberprensa*, May 10. http://cyberprensa.com/modules.php?name=Sections&op=viewarticle&artid=714. Accessed 2 Nov 2012.

Bratti, M.C., A.C. Rodríguez, M. Schiffman, et al. 2004. Description of a seven-year prospective study of human papillomavirus infection and cervical neoplasia among 10.000 women in Guancaste, Costa Rica. *Revista Panamericana de Salud Pública* 15(2): 75–89.

Castro Fernández, J.D. 2002. Costa Rica ¿es impune la experimentación en seres humanos? (In Costa Rica, is there impunity in human research implementation?) *Revista de Medicina Legal (Costa Rica)* 19(2): 103–116. http://www.scielo.sa.cr/scielo.php?pid=S1409-00152002000200012&script=sci_arttext. Accessed 2 Nov 2012.

CONIS. 2005. Informe. Legal affairs division DAR-RC-192-05, January 21.

Herrero, R., M.H. Schiffman, C. Bratti, et al. 1997. Design and methods of a population-based natural history study of cervical neoplasia in a rural province of Costa Rica: The Guanacaste project. *Revista Panamericana de Salud Pública* 1(5): 362–375.

Herrero, R., A. Hildestein, C. Bratti, et al. 2000. Population-based study of human papillomavirus infection and cervical neoplasia in rural Costa Rica. *Revista Panamericana de Salud Pública* 92(6): 464–474.

León González, F., and I. Vargas Navarro. 2006. Los derechos fundamentales de los seres humanos sometidos a experimentación u observaciones con fines experimentales, en centros hospitalarios,

educativos u otros, y la normativa costarricense (The fundamental rights of humans who participate in experiments or in observational studies conducted in hospitals, educational and other centers and the Costa Rica normative). Thesis, Universidad de Costa Rica.

Masís Figueroa, J., Contraloria General FOE-SA-159. 2003. Letter to the President of the CCSS Board (Eliseo Vargas García) about Informe No. DFOE-SA-2003 sobre el seguimiento de las diposiciones giradas en el informe FOE-SA-2/2001 (Report No. DFOE-SA-6-2003 on monitoring the regulations contained in Report FOE-SA-2/2001).

Mora Ramírez, A. 2006a. Costa Rica: Arias sabía de investigaciones de ministra para transnacionales farmacéuticas (Costa Rica: Arias knew that the new minister had conducted research for multinational pharmaceutical companies). www.informa-tico.com/. July 3.

Mora Ramírez, A. 2006b. Una Ministra empleada de la Gran Farma (A Minister of Health employed by Big Pharma). www.informa-tico.com/. May 22.

Páez Montalbán, C.A. 2005. Informe preliminar a la Junta Directiva del Colegio de Médicos sobre el llamado Proyecto Epidemiológico Guanacaste (PEG) (Preliminary report to the Board of Directors of the Medical Society on the Epidemiological Project Guanacaste (PEG)). May 29.

Proyecto de Guanacaste. n.d. www.proyectoguanacaste.org Accessed 10 Aug 2010.

Robles, S.C., and M. Roses Periago. 2004. Guanacaste, Costa Rica: A landmark for cervical cancer prevention. *Revista Panamericana de Salud Pública* 15(2): 73–74.

Vargas Carmona, E. 2005. Epidemia de Ensayos Clínico (Clinical Trials Epidemics). *La Pregonera* no. 5, November. http://cibersivas.net/pregonera/inicio.htm

WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre). 2009. Human papillomavirus and related cancers in world. Summary report 2009. Available at: www.who.int/hpvcentre or http://apps.who.int/hpvcentre/statistics/dynamic/ico/country_pdf/XWX.pdf?CFID=3797695&CFTOKEN=25736140. Accessed 10 May 2010.

Chapter 10
Ethical Guidelines for Clinical Trials in Mexico: Theory and Practice

Emma Verástegui and Edith Váldez-Martínez

10.1 Introduction[1]

This chapter examines several aspects related to clinical trials of pharmaceuticals in Mexico, including the number and characteristics of the trials, their regulation, and the challenges to be overcome to achieve compliance with international ethical standards and the protection of trial participants. Mexico, like other Latin American countries, faces many social and economic problems. Expenditures on health are relatively low (6.6 % of the Gross Domestic Product in 2006) (WHO 2009), and the health system is fragmented, highly politicized, and the demand for medical attention has increased. Although access to health services is a constitutional right, there is great inequity in access to medical care, and a high percentage of the population is not able to obtain needed medications.

Salaried employees and their families have good health care coverage through the various social security institutes. According to the Federal Ministry of Health, the rest of the population – almost 60 million persons – have access to health care

[1] This chapter was written in 2010 and since then there have been significant changes in clinical trial regulation. COFEPRIS has implemented a Clinical Trial Register [REGISTRO NACIONAL DE ENSAYOS CLÍNICOS (RNEC)] http://www.cofepris.gob.mx/AS/Paginas/Ensayos%20Cl%C3%ADnicos/Registro%20Nacional%20de%20Ensayos%20Cl%C3%ADnicos%20%28RNEC%29/Registro-Nacional-de-Ensayos-Cl%C3%ADnicos-%28RNEC%29.aspx. And the National Commission of Bioethics, promoted a Reform of the Ley General de Salud, and standardized the conformation of research ethics committees to meet international regulations. http://www.conbioetica-mexico.salud.gob.mx/interior/registrocomites/cei.html

E. Verástegui (✉)
Palliative Care, Senior Attending Physician, Instituto Nacional de Cancerologia, Mexico DF, Mexico
e-mail: everasteguia@incan.edu.mx

E. Váldez-Martínez
Coordinacion de Investigacion en Salud (en el IMSS), Instituto Mexicano de Seguro Social (IMSS), Mexico DF, Mexico

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_10,

and medicines through the Popular Health Insurance (*Seguro Popular*) that is mostly financed by the federal government and implemented through the states' governments[2] (Chertorivski Woldenberg 2010). For the four poorest income deciles, enrollment in the Popular Insurance is free. Independent researchers have not been able to verify the number of persons affiliated to the Popular Insurance scheme. The Popular Insurance provides access to more than 300 medications but it is known that access to pharmaceuticals varies by states, and the availability to several drugs is often unpredictable. In practice those covered by Seguro Popular continue to invest a substantial proportion of their meager income in the purchase of medicines.

10.2 An Attractive Country for Clinical Trials

Mexico is a very attractive country for clinical trials, for the following reasons:

1. As mentioned, a high proportion of the population has limited access to medical care and medications. With a national population of 110 million people, many low income Mexicans are willing to participate in clinical trials to receive free medications
2. There are specialized and well equipped medical centers with physicians and researchers who have received excellent training in prestigious locations in Mexico and abroad
3. There is an increase in chronic conditions in Mexico (cardiovascular, diabetes, and cancer), and the pharmaceutical industry is looking for new treatments for these conditions
4. As will be discussed later, the regulatory system and the rules governing the implementation of clinical trials are very weak
5. The proximity of the USA to Mexico, and the North American Free Trade Agreement (NAFTA), facilitates business relationships between the two countries

10.3 Clinical Trials in Mexico: Statistics and Location

Over the years, many attempts have been made to establish a register of the number and categories of research projects taking place in the country. According to Article 10 of the Regulations for Health Research of 1987 (De la Madrid 1987):

> . . . to Coordinate and Promote Scientific Development and Technology. . . the Ministry [of Health] will publish formal rules for institutions where research will take place, and for the registration and monitoring of projects

In 2010, the proposed register had not materialized, and there was no official record of the number of studies with human subjects that had taken or were taking place in Mexico.

One obvious information source should be the Federal Commission for Protection against Health Risks (COFEPRIS), the agency that regulates pharmaceuticals.

[2] The country of Mexico is made up of 31 states and the Federal District (DF – Distrito Federal).

Table 10.1 Number of clinical trials of medications in Mexico 2005–2009

	2005	2006	2007	2008	2009
Number of registered clinical trials	160	199	187	204	164
Phase I	2	4	4	3	4
Phase II	32	56	52	42	33
Phase III	110	135	95	132	93
Phase IV	21	16	34	28	24
Sponsored by:					
Pharmaceutical industry	158	172	166	192	138
NIH and other federal agencies in the USA	0	4	3	1	3
Universities/Organizations	3	30	22	16	20
With placebo (in study title)	86	79	80	120	75
Studies in children (0–17 years)	15	23	28	22	19

Source: www.clinicaltrials.gov

Note: Some studies are sponsored by more than one entity and can include more than one Phase

All clinical studies must be authorized by this agency, which therefore should have all the information about clinical trials. Unfortunately, COFEPRIS does not publish any information about clinical trials on its web page; not the number of trials, the number of participants, the companies sponsoring the trials, the names of the principal investigators, the products studied, the phase of the approved trials, or the participating institutions. It is also impossible to identify the protocols that have been rejected.

COFEPRIS publishes instructions on how to request information, but our application for information was unsuccessful. Requests for information on clinical trials must be made in writing and delivered to the offices of the Commission. In October 2009 we requested basic information which any researcher or citizen has the right to know; we did not ask for anything approaching an industry secret, but we did not receive an acknowledgement to our request. The impossibility of obtaining information is due to the inefficiency and lack of transparency at COFEPRIS, which does not permit access to their database and is in non-compliance with the international codes and declarations related to ethics in clinical research.

We used the USA federal register, clinicaltrials.gov, to obtain basic information on the clinical trials conducted Mexico, although as it has been discussed in (Chap. 3) this register has limitations. Phase I and many Phase IV studies are not always registered, and the records prior to 2006 were less reliable and tended to be incomplete. Within these limitations, Table 10.1 shows the number, type, and sponsors of the clinical trials of pharmaceuticals that took place in Mexico between 2005 and 2009.

Data from various Mexican organizations can complement the information from the US federal register. In 2006, the Coordinating Commission for the National Institutes of Health and High Specialty Regional Hospitals (CCINSHAE)[3] had

[3] The Coordinating Commission is a highly reputable administrative unit within the Federal Ministry of Health. Its purpose is to coordinate medical and hospital services to reduce the complications of rare illnesses. It brings together highly specialized human resources, equipped with advanced technology, who work in very expensive and specialized centers. Its scope includes 12 National Institutes of Health, which focus on conducting scientific health research, training

Table 10.2 Clinical studies according to AMIIF survey

Year	Number of patients participating
2005	51,000
2006	63,000
2008	87,000
Year	Cost in thousands of Mexican pesos
2005	850,000
2006	1,000,000
2008	1,590,000
Institutions conducting research:	Number (% of total)
Public	1,050 (84 %)
Private	200 (16 %)
Number of areas of therapeutic interest:	18
Number of researchers:	1,025
Number of protocols 2005–2008:	500

Source: Encuesta de investigación clínica AMIIF, 2006, data on file Asociación Mexicana de Industrias de Investigación Farmacéutica, Investigación para la vida AMIIF, 2010

registered 2,354 research protocols, approximately 60 % (1,412) being clinical trials sponsored by the pharmaceutical industry.

Some clinical trials last for more than 1 year and this number includes an unknown number of studies approved in previous years. Despite this, the number of studies reported by the Commission is much higher than the number obtained in clinicaltrials.gov. The Commission may also include clinical trials with medical devices and those using different surgical techniques, epidemiological studies, and a large number of Phase 4 studies, which are not included in clinicltrials.gov. Even if the non-pharmaceutical trials are subtracted, it still appears that the number of trials registered with the Coordinating Committee is much greater than those registered with the FDA.

Similarly, the data from other Mexican institutions do not distinguish between clinical trials of medications, studies of medical devices or surgical procedures, or socio-medical research. The Coordination of Medical Research of the Mexican Institute of Social Security (IMSS) registered 2,580 research protocols in 2006 and 2,372 protocols in 2008, of which an estimated 30 % (774 in 2006 and 712 in 2008) were clinical trials sponsored by the pharmaceutical industry – again, higher numbers than those registered by the FDA.

Most of the clinical trials are multicentric and international. Clinicaltrials.gov provides the number of patients to be enrolled in each study, but not their distribution by country. Table 10.2 shows data from the Mexican Association of Industries of Pharmaceutical Research (AMIIF), which presents the number of patients included in clinical trials sponsored by the pharmaceutical industry in 2005, 2006, and 2008; the total number of clinical trials, the number of participating researchers, and the industry-provided estimated cost of the studies (AMIIF 2010).

qualified health personnel, and providing specialized medical services; six Regional Specialty Hospitals and six Federal Referral Hospitals are located in Mexico City and surrounding states.

According to this source, only 500 studies were conducted during those years, while the FDA registered 563 studies for the same period. AMIIF data could also include Phase IV trials, which would not be registered by the FDA (see Table 10.2).

While the number of trials has decreased (see Table 10.1), Table 10.2 shows that the number of participants has increased, signifying that the number of participants per trial has increased. Studies were conducted in 1,250 sites; an average of 2.5 sites per trial.

Most clinical trials (84 %) took place in public institutions. There is no precise data of their distribution between the Ministry of Health and Social Security (IMSS) facilities, but it is known that before 2009 most pharmaceutical trials took place in the hospital network of the Ministry of Health, especially in the 12 decentralized National Institutes of Health.

It is easier to recruit patients in the Institutes of the Ministry of Health than in the IMSS facilities. The Ministry of Health provides medical care to people in poor socio-economic circumstances, without access to the Social Security hospitals. The following example suggests that access to medications is an attraction for clinical trial participation. In one Ministry of Health hospital, the number of women recruited in clinical trials with a breast cancer drug declined rapidly when the Ministry of Health included breast cancer treatment in the Popular Insurance scheme. Patients in the social security system (IMSS) are entitled to receive all medications free of charge, and were less likely to take part in clinical trials. In the case of illnesses or conditions without effective treatment, the willingness to participate in clinical trials is the same across all social classes.

The high number of researchers in the National Health Institutes (which serve low-income clients) is another attraction for the industry to conduct clinical trials in the Ministry of Health facilities. Researchers welcome the opportunity to conduct clinical trials because they have access to research funds and equipment donated to the hospitals by the pharmaceutical companies; they see the possibility of being published in international journals and participating in international conferences at industry expense, and many receive additional income for conducting these studies. These incentives are difficult to refuse. They explain the researchers' willingness to accept the conditions imposed by the pharmaceutical industry in the implementation of clinical trials.

10.4 Research Regulations and Their Implementation: The Role of COFEPRIS

This section will briefly examine the existing regulations in Mexico for clinical trials, identify areas of weakness, and evaluate compliance with the standards. The 1984 General Health Act (*Ley General de Salud*) (Cámara de Diputados del Congreso de la Unión 1984) and the subsequent 1987 regulations govern clinical trials. Title V of the Law, Articles 96–103, established the requirements for research, ethics and biosafety committees, mandated the establishment of a register of all studies, called for all studies to comply with the necessary standards to conduct valid scientific and ethical research, specifically stated that consent must be obtained in writing, and ordered all studies to be authorized by the health authorities.

The 1987 Regulation of the General Health Act for Health Research (RLGSIS) includes more detail on the manner and conditions that need to be fulfilled when conducting clinical research in Mexico. The Regulations emphasize respect for the dignity of the individual, the protection of participant rights and well-being, and require the informed consent of the participant (De la Madrid 1987).

In the General Health Act and in RLGSIS it is possible to identify elements of the Declaration of Helsinki but without making a direct reference to it. However, although both the Medical College of Mexico and the National Federation of Medical Colleges in Mexico (FENACOME) were admitted to membership in the World Medical Association in 1994, in this chapter we have highlighted several instances where the Mexican regulations are not properly aligned with the Declaration of Helsinki.

The Mexican Social Security facilities,[4] especially those belonging to IMSS, have standards and procedures governing research. Their clinical trial regulations allow for a more demanding approval process. Pharmaceutical companies see the IMSS procedures as "delaying research development" (Interview 2010a). Patients of IMSS and other Social Security institutes have free medical attention and medications, which makes it more difficult to recruit patients for clinical trials.

In 2001, the federal government created COFEPRIS, a decentralized agency of the Ministry of Health with technical, administrative, and operative autonomy. The Health Authorization Commission of COFEPRIS has the responsibility of authorizing clinical research with humans, establishing safety measures, and developing administrative sanctions in case of non-compliance with the regulations. It is involved with various aspects of clinical trials, such as protocol approval and authorization and the maintenance of the clinical trials register. The Commission must approve the informed consent process, the researcher's manual of procedures, the written information given to patients, the information to be used for participant recruitment, and all the information provided by the pharmaceutical company when requesting authorization to conduct the clinical trial. Any change in the principal investigator or modifications to the protocol must also be approved by the Commission.[5] The Health Authorization Commission includes committees such as that for New Molecules (SSA 2012) (see Fig. 10.1)

The Committee for New Molecules is an advisory board and its duties include:

1. Reviewing clinical trial protocols and advice on the approval or rejection of a proposed study
2. Providing comments and recommendations when medications already on the market seek approval for new therapeutic uses and Phase III or IV trials are requested to assure medication safety
3. Promoting cooperation between institutions and international agencies for the exchange of information about research development
4. Suggesting improvements in research strategies, evaluation, and follow-up of adverse effects arising during the clinical trials

[4] In addition to the IMSS, a number of labor unions have their own social security schemes that include health facilities for their beneficiaries. Among these, the most important are the union of state workers and the union of PEMEX, the national oil company.

[5] These functions have recently been changed.

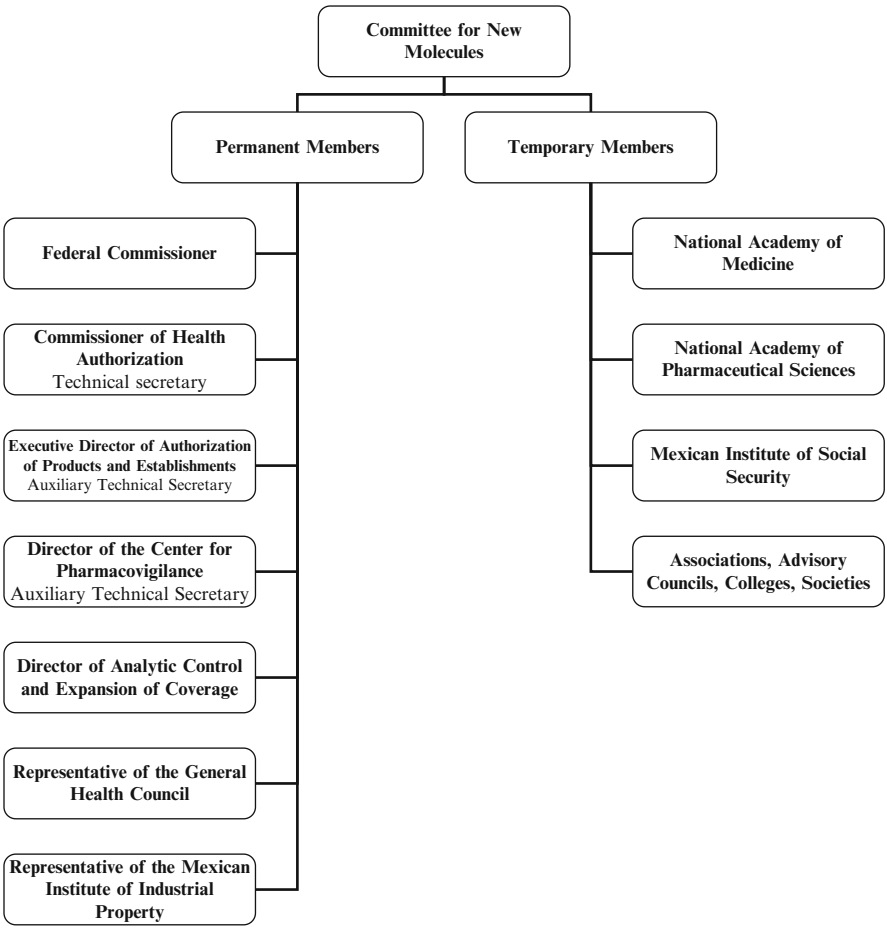

Fig. 10.1 Configuration of the Committee for New Molecules (Source: Mexican Government. Secretaría de Salud 2008 de México)

10.4.1 COFEPRIS Performance

The 2006 report published by EULABOR (Latin American and European Systems of Ethics Regulation of Biomedical Research) (Soberón et al. 2006) and written by the National Bioethics Commission – an independent agency created by Presidential Order – presented a demolishing picture of COFEPRIS performance. According to the report, in 2005, COFEPRIS was notorious for its lack of personnel with training in ethics. It also stated that COFEPRIS was not responsible for the ethical review of protocols, it did not have an ethics committee, its officials only reviewed aspects of the protocol that they selected without any pre-determined criteria, and potential conflicts of interests that had to be declared were not mentioned.

The work of COFEPRIS's officials was simply to fulfill an administrative task including aspects such as confirming that the protocol had an informed consent form that had been authorized in the institution where the study would take place by the institutional ethics committee, that the people conducting the trial had the necessary academic preparation, the project had a reasonable timeline and was providing all the necessary resources, and that it met the other requirements established in the Guide for the Presentation of Applications (Soberón et al. 2006; Valdez-Martínez et al. 2008).

Although COFEPRIS did not supervise institutional ethics committees, authorizing a protocol implicitly guaranteed that the clinical trial complied with ethical principles and that, during the trial, participant confidentiality would be respected and safety measures would be in place to protect the well-being of the participants. The EULABOR report discussed the shortcomings of COFEPRIS regarding the registration and monitoring of the ethics committees. The report suggested that COFEPRIS should not approve any clinical trial that was not approved by an ethics committee registered in the COFEPRIS database, but this suggestion received no action. The authors of the report pointed out that although COFEPRIS had existed for 5 years, it had failed to explain to those involved in clinical trials some basic procedures such as how to register ethics committees, or their obligation to do so. There were cases where ethics committees had asked how to register, but the Ministry of Health could not explain how they should do it.

According to the National Chamber of the Pharmaceutical Industry (CANIFARMA), the Committee for New Molecules uses exclusively industry information, their work is opaque, secretive, and does not request external assistance to improve its convoluted decision-making or provide feedback. CANIFARMA considers the work of this committee to be bureaucratic rather than scientific (Interview 2009a).

In 2007, the Health Authorization Commission (*Comisión de Autorización Sanitaria*) recognized the need to speed up the approval process for clinical trials. However, the added workload for the renewal of the market authorization of medicines, which became mandatory more recently, together with the increase in the number of clinical trial protocols for review has caused the approval process to remain slow. In 2009 a high official of COFEPRIS reported a delay in the authorization of at least 60 clinical trials that had been submitted more than one year earlier. That same year, COFEPRIS was not able to either supervise or do any follow up of clinical trials. In July, 2010, the Committee for New Molecules had accumulated 300 protocols and only had five persons to review them (Interview 2010b). Figure 10.2 presents two photographs of the document files accumulating in COFEPRIS, illustrating the disorder and inefficiency of the agency.

Recently, to simplify procedures and accelerate approval of clinical research, COFEPRIS administrators signed agreements with several institutions for a COFEPRIS representative to be present during the ethics committee discussions in the institution where a clinical trial was to be conducted. If the institutional ethics committee approved a study, the presence of the COFEPRIS representative meant that the study would be automatically accepted by COFEPRIS. Annex 1 is the copy of a

Fig. 10.2 Views of the Office of Health Authorization, COFEPRIS

Table 10.3 Length of time for clinical trial approval

Activity	Length of time required (average)
Translation of protocol	2–3 weeks
Approval by Ethics Committee	4–6 weeks
Approval by COFEPRIS	6–8 weeks

letter from the Commissioner of Health Authorization, COFEPRIS, to the Director of the National Cancer Institute confirming the implementation of this procedure. Although there is no information available on this new strategy, according to statements from some pharmaceutical manufacturers the time needed for the administrative process has remained unchanged at 3 months or longer (see Table 10.3).

The health institutions, the ethics committees, the pharmaceutical industry, and other agencies involved in clinical research are not happy with the regulatory activities of COFEPRIS. Apart from the notorious inefficiency and lack of transparency of COFEPRIS, other problems contribute to regulatory weakness. The regulation of clinical research with humans in Mexico has not been updated in more than 20 years; while there have been many important changes in research in general and in clinical trials in particular during this time.

It is necessary to standardize laws and regulations based on those established in international agreements. Mexico has not done so, and maintains that its policies do not have to be influenced by external agents or institutions. Some of the discrepancies with international regulations are as follows: according to Good Clinical Practices, ethics committees should have at least five members whereas Mexico only requires three members; the President of the committee should not be affiliated with the institution to avoid conflict of interest – not the case in Mexico, and there is also discordance in time limits to report adverse effects.

Mexican authorities have expressed interest in implementing clinical trials financed by the pharmaceutical industry. Understanding that the industry requires a more efficient regulatory process so that studies are completed as soon as possible, solutions have been proposed, which seem directed towards weakening regulations

even further instead of reducing bureaucratic inefficiency. For example, a Ministry of Health document published during the administration of President Fox (2000–2006) states (Enriquez Rubio et al. 2005):

> . . . it is necessary to have a regulatory framework that encourages rapid decisions from the research, ethics, and biosafety committees; accelerates review and approval of research protocols by the health authority, either with the participation of external reviewers of the health institutions or authorized third parties to make Mexico more competitive in clinical pharmaceutical research

This approach satisfies the industry's request for speeding up the approval of clinical trials, but ignores the need to protect the rights of participants. It could be suggested that protection of study participants would improve the quality of the information obtained.

10.4.2 A Failed Attempt to Regulate Clinical Trial

The EULABOR report indicated that Mexico had no specific official standards for health research because the regulations of 1988 (313, 314, and 315) had been rescinded by the adoption of the Federal Act on Metrology and Standardization (Soberón et al. 2006:27). Moreover, regulations 315–317 in the new Law were written to regulate research in general rather than the ethical aspects of clinical studies (Soberón et al. 2006:27).

To clarify this situation, in 2007 the Subsecretary for Innovation and Quality at the Ministry of Health issued a Draft Regulation (NOM-012-SSA3-2007) to establish criteria for conducting health research with human subjects, including clinical trials. The preparation of this draft document involved representatives from public and private research institutions during a period of 3 years[6] (Secretaría de Salud y Asistencia 2007). To achieve consensus, the Draft was discussed for nearly 2 years

[6] General Health Council, Ministry of Health, Subsecretary of Innovation and Quality, Directorate General of Quality and Health Education, Coordinating Commission of National Institutes of Health and Specialty Hospitals, representatives of 11 National Institutes of Health, Mexico General Hospital, Dr. Manuel Gea González General Hospital, Federico Gómez Children's Hospital of Mexico, Juárez Hospital of Mexico, National Medical Arbitration Commission, National Health Council, Institute of Security and Social Services for State Employees (ISSSTE), National Defense Ministry, National Institute of Statistics, Geography and Informatics, Ministry of Public Education, Directorate General of University Higher Education of the Subsecretary of Higher Education, National Council of Science and Technology, National Autonomous University of Mexico, National Polytechnic Institute, National School of Medicine and Homeopathy, Anahuac University, La Salle University, Mexican Foundation for Health (not-for-profit organization), National Association of Private Hospitals (not-for-profit organization), National Chamber of the Pharmaceutical Industry (not-for-profit organization), Angeles de Las Lomas Hospital (Anonymous Society of Variable Capital), Cowdray American British Hospital (not-for-profit organization), Medical South Hospital (Anonymous Society of Variable Capital), Spanish Benevolent Society (not-for-profit organization).

in meetings organized by the Federal Commission for Regulatory Improvement (COFEMER), an autonomous Federal agency within the Ministry of Economics whose objective is to guarantee transparency in the development and administration of regulations and that these may produce greater benefits than costs for society. From August 2008 to March 2009, COFEMER invited commentary from academic institutions, public health agencies, and other organizations which could be affected by the regulations. The only responses came from the National Chamber of the Pharmaceutical Industry (CANIFARMA), contract research organizations (CROs), and transnational pharmaceutical companies (Novartis, AstraZeneca, and GlaxoSmithKline).

Although the intent was to reach consensus, differences persist among the ethics committees, which operate according to Good Clinical Practices, the international pharmaceutical industry, and CROs. Even some COFEPRIS executives acknowledge major shortcomings of these long-awaited standards (Interview 2010c).

In January, 2010, important changes were to be made by the COFEPRIS Health Authorization Commission. The new Commissioner (a medical pharmacologist) seemed to have a clear vision of the challenges faced by this Commission, including the need for:

1. Efficient regulation of clinical trials, and the various people and organizations who conduct them (ethics committees, pharmaceutical industry, CROs, etc.)
2. Improvements in the register of ethics committees and its regular updating
3. Updating the clinical trial registers, and synchronizing their procedures
4. Improving the content of information available on the COFEPRIS web site

Without a clear explanation, the new Commissioner was replaced after 4 months, before he was able to make changes. The COFEPRIS web site still has minimal information. Searching for Clinical Trials, there are no links to information about regulations, about ethics committees, nor to a clinical trial register.

10.4.3 Lack of Pharmacovigilance

Mexican Law requires researchers to report suspicious adverse reactions occurring during clinical trials. These reports are generally made by personnel of the pharmaceutical industry or the Contact Research Organizations (CROs), whose responsibility is to monitor the implementation of the trial. Interviews with clinical trial monitors revealed that, in their experience, the reports of serious adverse reactions in clinical trials sent to COFEPRIS serve only to fulfill an administrative requirement (2010b).

Checking with the pharmacovigilance unit of COFEPRIS, there were no available reports of severe adverse reactions during the implementation of clinical trials. The lack of information at COFEPRIS contrasts with the number of adverse reports sent to the ethics committee of the National Cancer Institute (NCI). For example, in

September, 2009, the NCI ethics committee reviewed 350 serious, adverse reactions reported internationally, and 17 serious reactions reported in their own institution related to ten multi-centric clinical trials. The lack of compliance by COFEPRIS with such important standards could have an impact on the quality and reporting on clinical trials and could facilitate the marketing of unsafe medications. The United States FDA, the European Medicines Agency (EMA), and the regulatory agencies of countries where sponsoring pharmaceutical companies have their head offices, should be made aware of these issues so that they can closely control these industries.

10.5 The Role of Contract Research Organizations

During President Fox's administration (2000–2006), the Ministry of Health considered the CROs to be (Consejo Nacional de Salud 2003):

> A strategy to speed up the administrative processes for research projects, encouraging the formation and registration of ethics committees in (CRO) for multicenter studies which could take place in physician's offices or small medical facilities. These ethics committees should function in accordance with the standards set by the National Bioethics Commission and the State Bioethics Commissions

The same document notes a need for accredited third parties to review and comment on pharmaceutical research projects for those who want more rapid – even if more expensive – ethical evaluation as part of the Health Authority approval process. The document also notes the desirability of developing a list of trained researchers to review the protocols of health institutes and universities, and implement – through CCINSHAE – a program to strengthen its infrastructure by identifying a group of researchers and centers able to develop closer links with the industry. No data is available to verify if this has taken place.

An additional program of some CROs and private research institutions is to facilitate recruitment into clinical trials by offering databases of patients with different health problems. How this information will be gathered is unclear, and could violate patient confidentiality standards.

From the COFEPRIS perspective, the CROs are commercial service firms, which are not obligated to register with COFEPRIS. Because of this, there is no information about the number of CROs or the quality of their operations in Mexico. There are ten major CROs operating in Mexico (Quintiles, Covance, PPD, ICON, Kendle, Parexel, PRA International, Omnicare, Clinical Research, MMatiss), together with smaller international companies and Mexican organizations. There was no Association of CROs in Mexico until recently, although there are CRO Associations at the international level as well as national CRO Associations in other Latin American countries. In April 2010, CRO-Alliance was established as an association of CROs in Mexico (Personal Communication 2010), but so far CRO-Alliance has not said if there is a code of ethics for its members to follow.

10.6 Ethics Committees

In accordance with the Regulations of the General Health Act for Health Research (RLGSIS), three committees must be established in health facilities where research with human subjects is conducted: a research committee, an ethics committee, and a biosafety committee[7] (Valdez-Martínez et al. 2008; Valdez-Martínez and Porter 2004, 2005), and they began to be established in 1984, in institutions conducting research with human subjects.

According to RLGSIS, the committees should have their own regulations. Legally, the Ministry of Health has classified the ethics committees as administrative units, and has charged them with the responsibility to protect people participating in medical research. In the organizational structure, the ethics committees report to the Director of their health institution, which goes against international ethical standards because of a possible conflict of interest. It is unclear if clinical trial budgets should be part of the information submitted to ethics committees.

There are no regulations related to either the composition or the operation of ethics committees. Research ethics committees must register with COFEPRIS, but, at present, registration is an administrative process requiring only a formal certificate of its constitution and the names and professional accreditation cards of its members. As indicated, the Regulations for Health Research (De la Madrid 1987) require only three committee members less than the five required as a minimum by Good Clinical Practices and other international guidelines (Red Panamericana para la Armonización de la Reglamentación Farmacéutica 2005). There is no available information on the total number of committees, their structure, work timetable, and avoidance of conflict of interest policies. There is no information on committee procedures for the protection of the human rights of participants, and the prevention of their exposure to unnecessary health risks.

The lack of information and clear operational guidelines has caused confusion about the role of ethics committees. Valdez-Martínez et al. (2008); Valdez-Martínez and Porter (2004, 2005) analyzed the structure, function, member qualifications, and activities of ethics committees, and found an ambiguity of functions – clinical ethics, research ethics – lack of qualifications, and possible conflicts of interest when including institutional managers on the committees. Committees did not see that the protection of study participants was a fundamental duty of an ethics committee.

Most ethics committees have been established in public hospitals of the Ministry of Health, serving the most vulnerable population in Mexico. There is very little information on the operation of ethics committees in Ministry of Health facilities, in private hospitals, or in the military hospitals where research takes place (Amor Villalpando and Sánchez Granados 2000). The committee members of a major research institute of the Ministry of Health identified problems with informed consent. Most participants in the clinical trials had poor reading skills, the clinical

[7] The ethics committees often are identified with different names in different institutions: ethics committee, committee for research ethics, bioethics committee, etc.

Table 10.4 Characteristics of private ethics committees

	ReMeDi (n.d.)	Clinba (n.d.)	CBIC (n.d.)	CEIIS (n.d.)
Years in operation:	7 years	No data	12 years	4 years
Based at:	Pachuca, Hidalgo	Guanajuato	Mexico, D.F.	Monterrey, Nuevo Leon
Meetings scheduled	Every 2 months	3 times × Month	Every 2 weeks	n/a
Procedures	ICH-GCP	ICH-GCP	ICH-GCP	ICH-GCP
Accreditation	COFEPRIS	COFEPRIS CNB	n/a	OHRP
Number of members	6 members	6 members	5 members	n/a

trial information provided for them was clinically complex and the informed consent document was more than 20 pages long. Members of the ethics committee were convinced that the patients would not understand the information and would be unable to provide true informed consent. The committee asked for the information to be re-written to be better understood by study participants, but the researchers rejected the request. To rewrite the information would delay the start of the clinical trial, and the researchers knew that the pharmaceutical companies reward researchers who recruit participants in the least amount of time.

In contrast to other health institutions in Mexico, IMSS has a formal, structured system for 120 ethics committees. The IMSS ethics committees are responsible for assessing both the ethical aspects and the scientific rigor of every research proposal conducted in the corresponding IMSS medical facility. The ethics committees operate in accordance with regulations published in the IMSS Manual (IMSS 2006), and all are registered with COFEPRIS. Even with the operating standards for the IMSS ethics committees and annual reports, quantitative and qualitative evaluation studies published in 2004 and 2005 report weaknesses in structure, composition, and functioning (Valdez-Martínez and Porter 2004, 2005). For example, the committees are predominantly composed of men, physicians, and administrators. Only one third of the committee members have any formal training in scientific research or research ethics.

The number of private for profit ethics committees is rapidly growing. The little that is known about these private committees is presented in Table 10.4. It will be useful to know for all of the committees the professional and ethical expertise of their members, the number of protocols they approve, the time they take to approve them, how many protocols are not approved, and if they oversee the implementation of the trials. The CBIC (n.d.) has reviewed about 800 protocols during its 12 years of existence and Clinba (n.d.) reviews protocols and carries out other activities related to clinical trials very much like any CRO. In its electronic page Clinba indicates that it takes 5 days to review a protocol (http://clinba.com/).[8]

[8] In addition to the private for profit committees mentioned we can add: Comité de Ética Independiente en Investigacíon Científica, Paracelso, Eicla and Cecype.

The ethics committees of 54 Mexican institutions are registered with the Office of Human Research Protections (OHRP) in the United States Department of Health and Human Services. The registration of the Ethics Committees in the OHRP does not guarantee that they will follow the regulations of OHRP.

Without uniform operating procedures, there are differences in the time needed for the committees to evaluate study protocols. The executive director of an international CRO said that some committees approve protocols in 2 days, while others may take 3 months (Interview 2009b). Protocols must be approved by the research ethics committee in each institution participating in multicenter clinical trials; the approvals are a bureaucratic or administrative process with no assurance that committees consider the safety of study participants or the quality of the clinical trials. The composition and characteristics of ethics committees are very important. When approving or rejecting research projects, consideration should be given to the community context and the broad effects of the study, issues that sometimes are forgotten by physicians. Committees with a majority of male clinicians may have less sensitivity to the perspective of vulnerable populations than committees with representation from both genders, as well as community members.

10.7 Participant Vulnerability and Other Ethical Questions

Participants in clinical trials in Ministry of Health facilities are recruited from vulnerable populations and may not fully understand that they are participating in an experiment and may not be able to interpret the informed consent papers (see Chap. 11). In general, these participants have not had much formal education and do not have many resources, so that participation in a clinical trial is seen as a way of obtaining needed medications. The social, economic, and educational situation of many study participants limit their ability to give truly informed consent, either because the information provided is not understood, or their economic circumstances lead them to enroll in the study so that they can access the medications for free instead of having to pay for the standard treatment. The situation is even worse when the recruitment is done by the patient's physician, and the latter receives a monetary incentive per patient recruited. In this situation, the patient might feel coerced into participation for fear of retaliation, and the recruiter might be most interested in personal gain than in the true interest of the patients.

No specific provisions exist to assure study participants that they will benefit from the results of the clinical trial. Given the high price of the new medications, usually protected by patents owned by pharmaceutical companies, trial participants and Mexicans have no assurance that they will have access to the medications – once they are commercialized – that Mexican citizens have help to discover.

The approximate cost of several medications studied in Mexico is given in Table 10.5. Given the number of trials in process and that more than half the

Table 10.5 Approximate cost of treatment with new therapies

Medication	Therapeutic indication	Cost (in US dollars)	Current studies in Mexico (July, 2010)
Ranibizumab	Macular degeneration	$9,288.43 6 injections first year	4
Trastuzumab	Cancer	$49,915.00 for 3 months	13
Bevacizumab	Cancer	$48,490.00 for 3 months	35
Sorafenib	Cancer	$4,246.00 for 4 weeks	7
Sunitinib	Cancer	$10,548.00 for 4 weeks	6
Temsirolimus	Cancer	$7,664.00 for 4 weeks	1
Remicade	Rheumatoid Arthritis and autoimmune diseases	$1,006.00 per dose 1 dose every 8 weeks (varies depending on the condition being treated)	5

Costs in Mexico were obtained by personal interviews by Emma Verástegui with specialists in the area, and are an approximation. FDA approved medications on sale to the public in Mexico. On line consultation, August 6, 2010. http://www.fda.gov/

patients of public institutions have a very low income, it is reasonable to conclude that less than 5 % of the uninsured population could access to these treatments. This is an issue related to the justice principle, which must be observed during clinical trial planning and implementation.

10.8 Conclusion

Ten years after the establishment of COFEPRIS, this regulatory agency has not been able to improve the protection of study participants nor to assure scientific quality in clinical trials. Although a national legal framework exists, there is a significant backlog in the approval of clinical trials, making it impossible to guarantee the well-being and the rights of Mexicans who participate in the studies. Laws and regulations of biomedical research have not been updated according to innovations that have taken place in the field. Other government agencies such as the National Bioethics Commission have lacked consistency in their policies and have been unable to improve the performance of the committees.

There is no national policy for the protection of study subjects, neither is it possible to obtain basic information about clinical trials nor the incidence of adverse events effects. The registration of clinical trials continues to be a simple administrative procedure with no way of knowing what happens in the review process, the number of ethics committee members involved, their qualifications, and the absence of conflicts of interest.

Serious flaws exist in the informed consent process, and the consent forms themselves are frequently not understandable by most of the Mexican population.

Commissions responsible for setting standards and regulating research with human subjects in Mexico should be composed of members who are morally

committed and knowledgeable about scientific research. They should also understand the issues involved when very vulnerable people are asked to participate in clinical trials of medications that will not be accessible to most of the population. One priority is to establish ongoing audits of the ethics committees with the goal of assisting them to improve their structure and performance. Instruction in ethics and research methodology is essential.

Ethics committees have a variety of problems. The experience and understanding of their members vary considerably. Committees function erratically, so much so that clinical trials approved by some ethics committees should be of concern if we take into account the following: (1) most public hospital patients have low levels of education and limited socio-economic resources; (2) the difference between agreeing to standard treatment and experimental treatment is that in many instances the first must be paid for by the patient and the second is free to patients since it is sponsored by the pharmaceutical companies; (3) in most cases, procedures are obscure and physicians and researchers have conflicts of interest due to potential economic and professional benefit from conducting clinical trials.

We need to add that in Mexico, among health professionals the culture of ethics does not have a solid tradition and committee members tend to be poorly informed about international policies on the composition and functions of an ethics committee.

Mexico is an attractive country for clinical trials, but almost 30 years after adopting the General Health Act and the Regulations of the General Health Act for Health Research (RLGSIS) the people of Mexico lack the certainty that their rights as participants in clinical research are being fully protected.

Annex 1

Letter from COFEPRIS to the National Cancer Institute explaining the new system of approval of research protocols

09/07/2013 12:39 99500895008 PAGE 01

COMISIÓN FEDERAL PARA LA PROTECCIÓN CONTRA RIESGOS SANITARIOS

Vivir Mejor

SECRETARÍA DE SALUD SALUD

"2009, Año de la Reforma Liberal"

OFICIO No. CAS/1/OR/6928/2009

México, D.F. a 03 de septiembre de 2009

DR. ALEJANDRO MOHAR BETANCOUR
Director General del Instituto
Nacional de Cancerología
Av. San Fernando No. 22
Col. Sección 16, Deleg. Tlalpan,
C.P. 14080, México, D.F.
Presente

Por este conducto, me dirijo a Usted para hacer de su conocimiento que esta Comisión Federal para la Protección contra Riesgos Sanitarios, designa al Dr. Omar Francisco Carrasco Ortega como representante de esta Comisión ante el Comité de Investigación y Ética del Instituto Nacional de Cancerología.

El nombramiento del Dr. Omar Francisco Carrasco Ortega implica la participación de la COFEPRIS en el procedimiento de autorización de protocolos por parte del Comité anteriormente citado, por lo tanto, cuando el Comité de Investigación y Ética del Instituto Nacional de Cancerología autorice un protocolo, simultáneamente lo estaría haciendo esta Comisión Federal, por lo tanto, no será necesario realizar trámite adicional ante nosotros.

Agradezco su valioso interés en participar en la investigación y el desarrollo de metodologías que aseguren la calidad de los servicios que el Gobierno Federal proporciona a la población.

Sin otro particular, le envío un saludo.

CAMARA NACIONAL DE LA INDUSTRIA FARMACEUTICA SET. 8 2009

SUFRAGIO EFECTIVO. NO REELECCIÓN.
COMISIONADO DE AUTORIZACIÓN SANITARIA

GUSTAVO A. OLAIZ FERNÁNDEZ

C.c.p. Lic. Miguel Ángel Toscano Velasco.- Comisionado Federal para la Protección contra Riesgos Sanitarios.- Presente.
Dra. Carmen González Almeida.- Comisión de Autorización Sanitaria.- Presente.
Dr. Guillermo Soberón Acevedo.- Presidente del Consejo de la Comisión de Bioética.- Carretera Picacho Ajusco No. 154, Piso 6, Jardines en la Montaña, C.P. 14210, Delegación Tlalpan, México, D.F.- Presente.
Ing. Jaime Urbe de la Mora.- Presidente de la Cámara Nacional de la Industria Farmacéutica. CANIFARMA.- Av. Cuauhtémoc No. 1481, Col. Sta. Cruz Atoyac, C.P. 03310, México, D.F.- Presente.
Ing. Jaime Pira k.- Presidente de la Asociación Mexicana de la Industria de Investigación Farmacéutica. AMIIF.- Av. Cuauhtémoc No. 1481, 1er. Piso, Col. Santa Cruz Atoyac, C.P. 03310, México, D.F., Presente.
Dr. Dagoberto Cortéz Cervantes.- Presidente de la Asociación Nacional de Fabricantes de Medicamentos. ANAFAM.- Av. Cuauhtémoc No. 1481, 2º. Piso, Col. Santa Cruz Atoyac, C.P. 03310, México, D.F., Presente.

Monterrey 33 Col. Roma, Del. Cuauhtémoc México, DF 06700
Tel. 5080 5200 ext.1485. www.cofepris.gob.mx

Translation of the body of the letter (written on September 3, 2009):

This letter will notify you that the Federal Commission for Protection Against Health Risks has appointed Dr. Omar Francisco Carrasco Ortega as its representative to the Committee for Research and Ethics of the National Cancer Institute.

The nomination of Dr. Omar Francisco Carrasco Ortega indicates the participation of COFEPRIS in the procedure to authorize protocols by the said Committee, by which means, when the Committee for Research and Ethics of the National Cancer Institute authorizes a protocol, simultaneous authorization is granted by the Federal Commission and it is therefore not necessary to conduct an additional review with this office.

I thank you for your valuable interest in participating in the research and development of methods to assure the quality of the services, which the Federal Government provides for the population.

(Signed)
Gustavo A. Olaiz Fernández
Commissioner of Health Authorization

References

Asociación Mexicana de Industrias de Investigación Farmacéutica (AMIIF). 2010. Encuesta de investigación clínica (Survey of clinical research) 2005–2008. México DF: AMIIF.

Amor Villalpando, A., and P. Sánchez Granados. 2000. Profesionalización de los Comités de Bioética intrahospitalarios (Professionalization of the bioethics hospital committees). *Revista de Sanidad Militar Mexicana* 54(2): 102–106.

Cámara de Diputados del Congreso de la Unión. 1984. Ley General de Salud (General Health Act). Diario Oficial de la Federación, February 7, México DF. http://sinais.salud.gob.mx/descargas/pdf/LGS.pdf. Accessed 2 Nov 2012.

CBIC. El Comité Bioético para la Investigación Clínica S.C. n.d. http://www.cbic.com.mx/. Accessed 2 Nov 2012.

CEIIS. Comité de Ética Independiente en Investigación Científica. n.d. www.ceiic.org. Accessed 2 Nov 2012.

Chertorivski Woldenberg, S. 2010. Aviso que establece los niveles de las cuotas familiares del Sistema de Protección Social en Salud para 2010 DOF.25-5- (Notice that establishes the family premiums for the System of Social Protection in Health for 2010). http://dof.gob.mx/nota_detalle.php?codigo=5143971&fecha=25/05/2010. Accessed 2 Nov 2012.

Clinba. Comité Independiente de Ética, Investigación y Bioseguridad del Bajío, S.C. n.d. http://clinba.com/. Accessed 2 Nov 2012.

Consejo Nacional de Salud. 2003. Acuerdo IX, 22, Febrero 27. México DF: CNS.

De la Madrid, M. 1987. Reglamento de la Ley General de Salud en Materia de Investigación para la Salud (Regulation of General Health Act related to health research). http://www.salud.gob.mx/unidades/cdi/nom/compi/rlgsmis.html. Accessed 2 Nov 2012.

Enríquez Rubio, E., C. Frati Munari, and E. González Pier. 2005. Hacia una política farmacéutica integral para México (Towards a comprehensive Mexican pharmaceutical policy). México DF: Secretaría de Salud, Comisión Federal para la Protección Sanitaria. www.respyn.uanl.mx/viii/3/contexto/politica_farmaceutica.pdf. Accessed 2 Nov 2012.

IMSS. 2006. Reglamento interior que del Instituto Mexicano de Seguridad Social (Internal rules of the Mexican Institute of Social Security). Diario Oficial, 16 September. http://www.encuentra.gob.mx/resultsAPF.html?q=Normatividad%20Institucional%202006&client=imss&ts=all&geo=0. Accessed 3 Nov 2012.

Interview with professionals of three transnational pharmaceutical companies, 18 November 2009a.

Interview with an executive director of an international CRO, 17 March 2009b.

Interview with the medical director of a pharmaceutical company, 21 May 2010a.

Interview with a professional staff of COFEPRIS, 20 July 2010b.

Interview with an executive officer of COFEPRIS, 6 February 2010c.

Personal communication, CRO's executive 19 April 2010.

Red Panamericana para la Armonización de la Reglamentación Farmacéutica. 2005. IV Conferencia Panamericana para la Armonización de la Reglamentación Farmacéutica. Buenas Prácticas Clínicas (IV Panamerican conference. Harmonization of pharmaceutical regulation. Good clinical practices) Dominican Republic, 2–4 March. http://www.paho.org/spanish/ad/ths/ev/bpm_antec-esp.pdf. Accessed 3 Nov 2012.

ReMeDi. Comité Bioético de Resultados Médicos Desarrollo e Investigación, S.C. n.d. http://www.remedi.org.mx/comite-de-etica/comite-de-etica.html. Accessed 2 Nov 2012.

Secretaría de Salud de México. 2008. Regulación de medicamentos en México (Pharmaceutical regulation in Mexico). http://new.paho.org/hq/index2.php?option=com_docman&task=doc_view&gid=127&Itemid=960. Accessed 2 Nov 2012.

Secretaría de Salud y Asistencia. 2007. Proyecto de Norma NOM-012-SSA3-2007 que establece los criterios para la ejecución de proyectos de investigación para la salud en seres humanos (Normative proposal to establish the criteria for the implementation of research studies involving human subjects). http://dof.gob.mx/nota_detalle.php?codigo=5117857&fecha=05/11/2009. Accessed 2 Nov 2012.

Secretaria de Salud (2012) Reglamento interior del Comité de Moléculas Nuevas (Internal rules of the Committee of New Molecules). Diario Oficial de la Federación 23 Feb http://www.diputados.gob.mx/LeyesBiblio/regla/n328.pdf Accessed 3 Nov 2012.

Soberón, G., D. Feinholz, and E. Cuellar. 2006. México: Situación y perspectiva del regulación ética y la protección a los sujetos de investigación. Reporte de trabajo para el Proyecto EULABOR (Mexico: Situation and perspectives on ethical regulation and pretection of human research subjects. Report for EULABOR). http://www.eulabor.org/docs/in_mexico.pdf. Accessed 2 Nov 2012.

Valdez-Martínez, E., A. Lifshitz-Guinzberg, J. Medesigo-Micete, M. Bedolla. 2008. Los comités de ética clínica en México: la ambigua frontera entre la ética asistencial y la ética en investigación clínica (Clinical ethics committees in Mexico: the threshold ambiguity between medical care and research ethics). *Revista Panamericana de Salud Publica* 24:85–90. http://www.scielosp.org/pdf/rpsp/v24n2/a02v24n2.pdf. Accessed 3 Nov 2012.

Valdez-Martínez, E., and D.H.J. Porter. 2004. Local research ethics committees of the Mexican Institute of Social Security: Results of a national survey. *Public Health* 118: 329–336.

Valdez-Martínez, E., and D.H.J. Porter. 2005. Understanding the structure and practices of research ethics committees through research and audit: A study from Mexico. *Health Policy* 74: 56–68.

WHO. 2009. Health expenditure: Total expenditure on health as % of gross domestic product, 2006. Ginebra: World Health Statistics, 112. http://www.who.int/whosis/whostat/EN_WHS09_Table7.pdf. Accessed 2 Nov 2012.

Chapter 11
Who Decides? Informed Consent for Cancer Patients in Mexico

Alonso Cerdán, Alejandro González-Arreola, and Emma Verástegui

11.1 Introduction

The Anglo-American model of applied ethics, notably as presented by L. Beauchamp and James F. Childress (2009), has dominated international bioethics. Many ethicists argue that there are fundamental ethical principles which should apply across all cultures and all nations, but the emphasis given to patient autonomy and informed consent (two fundamental ethical principles) can seem very peculiar for many other cultures.

According to the American Medical Association (2008), informed consent is:

> . . . a process of communication between a patient and physician that results in the patient's authorization or agreement to undergo a specific medical intervention

The College of Physicians and Surgeons of the Canadian province of Alberta (2002) considers that a patient competent to give consent (Grubb et al. 2003:89):

> . . . if [the patient] is capable of understanding what is involved in the medical treatment, including the procedure itself, its consequences and the consequences of non-treatment

Several studies have shown that the western values behind the principle of patient autonomy cannot necessarily be applied in a universal manner (Blackhall et al. 2002). Young (2001) describes the western principle of autonomy as demanding self-determination, assuming an individual subjective conception of the good,

A. Cerdán (✉)
Project Director of GESOC and Young Leaders Scholarship Recipient of the World Bank, GESOC A.C., Mexico DF, Mexico
e-mail: acerdan@gmail.com

A. González-Arreola
Director of GESOC, Mexico DF, Mexico

E. Verástegui
Palliative Care, Senior Attending Physician, Instituto Nacional de Cancerologia, Mexico DF, Mexico

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_11,

and promoting the value of individual independence, and Blackhall et al. (2001:59) makes the point that:

Ethnicity was the primary factor related to attitudes towards truth telling and patient decision making.

In many countries, the principal of autonomy is applied by involving the family in decision-making (Fan 1997). In this process of collective decision-making, families receive information about the patient's diagnosis and make the treatment decision, often without consultation with the patient who, for cultural reasons, has not been told the diagnosis.

In Mexico, the right to health was established in the Constitution, although, in the fragmented Mexican health system, half of the country's poorest people do not belong to the Social Security system. Many of them are instead affiliated with the Popular Insurance program (Seguro Popular), which leaves them with uncertain access to health services and some medications. Informed consent is an ethical obligation and a legal requirement specified in the Mexican Health Act (Secretaría de Salud 2007).

The National Cancer Institute (INCan) is an autonomous center of the Ministry of Health (SS). INCan is a high technology research center, providing specialized care to people with cancer. Most patients are low income, and not covered by social security. As an important cancer research center, INCan attracts a large number of clinical trials. In 2008, INCan evaluated approximately 40 clinical trial protocols sponsored by the pharmaceutical industry. Almost all patients with lung cancer were enrolled in clinical trials, followed by a large proportion of patients with breast cancer, ovarian cancer, kidney cancer, prostate cancer, leukemia and lymphoma. According to a member of the INCan ethics committee, approximately 40 % of INCan patients are participants in clinical trials sponsored by the pharmaceutical industry.

INCan receives public financing, and patients' fees vary depending on their socio-economic level. One percent of hospital patients receive free care due to their extreme poverty, while others pay on a sliding scale according to their family income. Medical care tends to be affordable but patients must also pay for other expenses which can be very costly, such as the price of medications (Secretaría de Salud 2001).

Given their economic worries, few patients ask about their illness and available treatment options. The wide social and educational gap – and frequently a cultural gap – between physicians and patients often results in poor communication, and patients tend to have difficulties understanding the information given by the physician (Kagawa-Singer 1996; Kleinman et al. 1978). For the same reasons, treatment recommendations are not communicated clearly between physician and patient.

Mexican law requires that the patient needs to be informed about his treatment options and needs to provide consent before participating in a clinical trial. The inherent characteristics of INCan patients (generally uninformed about health) and the communication problems between physicians and patients contribute to the lack of patients' understanding of the course and prognosis of their illness, their treatment options, and the risks and benefits related to each. Incomplete understanding has important ethical implications, and may have significant consequences in the acceptance and compliance with treatment, the economic impact, or the decision to

participate in a clinical trial. Mexico has given little attention to these concerns and there is a risk that informed consent is neither free nor informed.

In clinical trials, communication problems may have other serious consequences. Informed consent is presented as a factor which guarantees participant protection during clinical trials, making the assumption that trial participants and/or their families understand the possible risks and benefits. If the participants and their families do not properly understand how to take the medication being tested, the results of the clinical trial will have little reliability.

This chapter describes patient perception of the information given to them by INCan physicians, together with the patient's ability to make conscious and informed decisions from the information received. The results of this study may be used to design a program to improve the relationship between physicians, patients and their families, and to increase patient/family understanding of the nature of the disease and its treatments. Study results could also be used to revise institutional policy for obtaining informed consent, to better protect the human rights of patients participating in clinical trials, and to improve the quality of data gathered.

11.2 Method

Initial interviews were conducted with hospital authorities, physicians, and social workers to document the medical and administrative requirements for admitting patients into the institution. From this information, a research instrument and an interview guide for focus groups were developed. The protocol was submitted for approval by the INCan Bioethics Committee.

To obtain epidemiologic and socio-economic data of INCan patients and to assure representative focus groups (Merton et al. 1956), a random sample was taken from the 3,735 patients who received treatment during 2007. Electronic hospital records were analyzed for 339 patients (95 % confidence interval, 5 % margin of error). Variables included in the study were diagnosis, age, gender, civil status (single, married, etc.), place of residence, years of education, occupation, monthly income, type of residence, and distribution of income (food, rent, services, etc.).

The socioeconomic information obtained from the patient records was reviewed by the INCan Department of Social Work to determine the socio-economic level of each patient and the corresponding treatment fees. There are seven levels based on the daily income. Level 1 is the equivalent of US$1.00 per day; Level 2 equals US $3.00 per day; Level 3 equals US$7.00 per day, and Level 7 equals a daily income of US$30.00 or more.

A semi-structured questionnaire was used to guide the focus group discussions around specific aspects of the medical and administrative information provided to patients. The questions were designed to explore the patients' perception and understanding of the information they received about their disease and their ability to use this information to make decisions about their treatment (see Table 11.3).

INCan social workers had previously drawn a random selection of patients for invitation to participate in focus groups. The focus groups were organized in a non-systematic manner. Each group was made up of eight patients who were either waiting for a consultation or who had received radiation treatment or chemotherapy on the day the group met. A social worker had previously explained the purpose of the group to each patient and had invited them to participate.

Patients who accepted the invitation to participate met in a small conference room. The sessions were informal, and began with a presentation by the coordinator explaining the purpose of the study. After assurances that the participation of each patient was voluntary, and guarantees of confidentiality and anonymity of information, verbal authorization to record the session was requested. The patients' verbal consent was recorded.

At the beginning, family (and/or household) members accompanying patients were allowed to be present at the back of the conference room. At the end of the first session, the patients interviewed were approached by their relatives, who also had comments relating to the questions discussed. For this reason, it was decided to form separate focus groups with patient's families. The invitation extended to participating families was also made in a non-systematic manner. Some family (and/or household) members were related to those participating in the patients' focus group, but the majority were not. A total of 32 patients (four groups of eight patients) and 16 family members (two groups of eight people) participated.

In each session the coordinator presented the topic of discussion to the participants and asked for age, place of residence, and diagnosis. Impartial questions were then asked to guide the group discussion. The comments were recorded, and notes were taken at the same time. Both the recordings and the notes were immediately transcribed and verified by the authors. The discussions focused on information about the process of obtaining informed consent and the roles of key personnel. Each session lasted for at least two and a half (2 and 1/2) hours. The transcribed material was analyzed using content analysis (Kipendorff 2004) to identify the different domain responses provided by each group, and the information was aggregated to obtain an overall picture.

Focus group participants did not receive any money for their participation, but were offered refreshments during the sessions as well as a small token (a pen, exercise book, and a plastic folder for their papers).

11.3 Results

11.3.1 Description of the Sample

Demography Electronic records of 339 patients who received care during 2007 were analyzed (9 % of all patients receiving treatment). INCan generally provides care for adults, and only 5 of the 339 patients analyzed were under the age of 18 years. The majority of patients (54 %) were between 40 and 70 years of age (Table 11.1).

Table 11.1 Demographic characteristics and diagnosis of the study sample

Number of patients		339
Age (years)	Median	48
	Range	17–91
Gender	Male	37.5 %
	Female	62.5 %
Place of residence	Mexico City and Mexico State	62 %
	Other areas in the country (Republic) of Mexico	38 %
Area of residence	Urban	47 %
	Semi-rural	34 %
	Rural	19 %
Tumor diagnosis	Cancers of the breast, cervix, and ovaries	36 %
	Gastro-intestinal cancers	17 %
	Skin (not melanoma)	9 %
	Prostate cancer	8 %
	Leukemia y lymphoma	7 %
	Cancers of the head and neck (throat and mouth)	7 %
	Other cancers	16 %

Female patients outnumbered male patients by a ratio of almost 2:1, which is probably explained by the high proportion of patients with cervical or breast cancers.

The INCan is located in Mexico City and most patients in the sample resided either in the Mexico City (also known as the Federal District with approximately 21 million people) or in the state of Mexico, which borders the city to the north and west. Although the country of Mexico has a network of cancer centers that provide treatment to uninsured patients in the 32 states of the Republic, 38 % of the patients in the sample resided in other states.

Approximately 47 % of the patients in the sample lived in urban areas, but urban housing in poorer neighborhoods in Mexican cities may lack basic services such as potable water. Patients living in rural and semi-rural areas represent 53 % of patients in this sample (Table 11.1).

Medical characteristics Data obtained from patient records revealed that the study included people with different types of tumors: breast and gynecological cancers (35 %); gastro-intestinal cancers (17 %); hematological cancers (17 %); prostate cancer (8 %), and skin cancers (7 %). Less frequent cancer types included cancers of the head and neck, lung, and testicles, etc. According to hospital authorities, the sample represented the incidence of cancers in patients receiving care at the institution (Table 11.1)

Education and occupation One fifth (20 %) of the patients in the sample had had no formal education. Of the remaining sample population, almost half (45 %) had 6 years or fewer in school, and only 6 % had completed high school or more.

INCan exists to provide care to the Mexican population not enrolled in the Social Security system. The sample reflects this population – 74 % of the sample were unemployed or had unpaid jobs. Only 3 % had work which required education or training.

Table 11.2 Socioeconomic characteristics of the study sample

		Percent
Years of education	No formal education	20
	1–6 years (primary)	45
	6–9 years	21
	9–12 years	8
	12 years or more	6
Occupation	Unemployed, or working without financial remuneration[a]	74
	Employment not requiring formal education	23
	Employment requiring education or training	3
Monthly family income	<$1,000 Mexican pesos[b]	7
	$1,000–3,000 Mexican pesos	55
	$3,000–6,000 Mexican pesos	28
	>$6,000 Mexican pesos	10
Proportion of income for food (monthly)	<$3,000 Mexican pesos	86
	$3,000–5,000 Mexican pesos	12
	>$5,000 Mexican pesos	2

[a]Including those employed in domestic service. Many women are forced to stop work due to cultural reasons

[b]The exchange rate varies between $10 and $12 Mexican pesos per US$1

Family monthly income Monthly income for the family as reported in the reviewed records is shown in Table 11.2. Almost two thirds (62 %) of the families of patients in the sample reported a monthly family income of less than US$300, with 7 % of families in this group receiving less than US$100 per month. According to our information, the income is distributed between food, rent, and other services, including transportation (Table 11.2). These expenses leave little or nothing for medical care or education.

11.3.2 Focus Group Interviews

Patients In the focus groups, patients responded to the questions (see Table 11.3) with a consistent interest in participating and a willingness to share their experiences. Answers to the first question showed two major areas of concern: (1) to have information about the stage of their illness and the possibilities for a cure, and (2) the possibility of being admitted into the hospital.

Responses to this question included:

> My major worry is to understand how advanced is my condition, because when you hear the word cancer your life stops. . . (Patient age 56, with breast cancer)

> I was very worried that they wouldn't admit me to the hospital; once I was admitted, I felt very calm and sure that I would be cured. . . (Patient age 67, with melanoma)

Table 11.3 Representative responses of focus groups

	Responses	
Questions	Patients	Families
1. Principal concerns during the first appointments at the institution	Stage of illness and possibility of cure	Stage of illness
	Possibility of being admitted to the hospital	Cost and duration of treatment
		Administrative requirements
2. What kind of information did you want to receive?	Information about the illness	Information about care in the home of the patient
	Administrative requirements	Treatment options and their costs
		The need for information about the illness without the patient being present, "to avoid greater worry for the patient"
		To receive information they in a language they can understand, without medical terminology
		To receive an explanation about the diagnostic processes for the illness
3. How long did it take you to understand your diagnosis and the type of treatment you would receive?	Answers varied, but none showed an understanding of the illness	A continuous process, in which the family needs to ask different questions at different stages of the illness
	Possibility of cure	
	The need for information about the illness and the results of laboratory tests	
4. Do you think that there were specific factors that made it easier for you to understand the information you received?	Information provided by the physicians, and information from other patients	Mostly information from other families in the waiting room
		Information from the physician
5. Do you think, after some time attending the institution, that there is a better way to provide the information you received?	Clear and direct information provided by the physician	Written information
	Information presented on posters	A 24-h telephone hot line
	The cost of hospitalization for surgery	Specific information about patient care, reaction to medications, deterioration or setbacks in health, and prognosis for the course of the illness
		Options for financial assistance

(continued)

Table 11.3 (continued)

Questions	Responses	
	Patients	Families
6. Are you familiar with the term "informed consent"?	All patients had signed an informed consent form	It was a part of the administrative process
	It was a requirement to be admitted to the hospital	
7. Do you have any additional comments?	Thanking the physicians and the institution	When anyone in the family has cancer, the whole family suffers
	A feeling of safety	

The information requested by patients (question 2) depended on the type of illness. Patients with breast cancer were anxious to have information; patients who had been undergoing treatment for a longer period or time or had spent more time in the hospital wanted more precise information; male patients were worried about their employment, and older patients were most concerned about the possibilities of a cure.

> I have been here for two years, and the treatments change often. I always feel ill after treatment, so... I want to know what is happening to me... (Patient age 20, with leukemia)

Only a few patients had questions about administrative procedures, the cost of treatment, or financial questions. Most patients had received treatment for several months or even years in the hospital.

There was no direct response to the question of how long it took them to understand their diagnosis and treatment options (question 3); all responses related to the possibility of being cured.

> They've given me all the tests, but I don't know anything; no-one has told me anything. They say I have a malignant tumor, but what I really want to know is if I am sick, or what is going to happen to me... (Patient age 63, with head and neck cancer)

> I don't know anything; after two years here I am desperate because I have already had many problems... I don't know what is going on. Somebody tells me something, but in a few days they say something else... (Patient age 60, with cancer of the uterine cervix)

In the initial response to the question about factors which improve patients' understanding about their illness, most patients said that they knew about their illness and that their physician had "clearly" explained the nature of their problem, its prognosis and treatment. On probing more deeply, however, the patients were not able to explain their diseases or the information given by the physician. Of the 32 patients participating in the focus groups, regardless of the knowledge of their disease and treatment options, not one could give specific information about the type of cancer they had, the stage of the disease, treatment options or the possibility of cure.

The following example is typical of the limited information understood by the patients. This patient knew that she had advanced cancer, but, repeating the information given to her by the physician, implied that science could not help her; it was all in the hand of God.

> Yes, I understand my disease. The physician told me that I had advanced cancer. What will happen to me, how long I shall live, I don't know, because the doctor said that we are not gods, and only God knows how this will end... (Patient age 45, with cancer of the uterine cervix)

The patients spoke of their illness as "an obsession", the only item of importance to them at this time.

In reply to question 4, most patients said that written information and videos helped them to understand their disease. They also felt that conversations with other patients were very useful.

All the patients said that they had signed an informed consent form (question 6), although they acknowledged having limited knowledge of its content and objectives. Most patients said that the document was more of a requirement for admission to the hospital.

> It doesn't matter to us what it is for, they told us to sign it and that was enough... (Response from one group of patients)

In response to question 7, which asked for additional comments related to any of the topics discussed, none of the patients had any complaints about their physicians. Instead, the patients were grateful for having been admitted to the hospital, and believed that the quality of care provided by the institution and the physicians was "the best". One 60-year old male patient cried as he said:

> I am thankful to be a patient at INCan...I am thankful for the care they have given me

There was dissatisfaction, however, about the information given to them by the physicians.

Families of patients Family participation in the focus groups was extremely valuable. These sessions lasted longer and revealed three major concerns: (1) the diagnosis and stage of the disease; (2) the cost of treatment, and (3) payment options. The financial aspects were most important for the families.

According to the families, the information provided by the hospital was confusing and insufficient in several ways. Most families wanted more information about how to care for the patient at home (Table 11.3), the need for an explanation about the diagnosis and procedures, and the treatment options and costs during the illness.

Some families said that the information given to them was often overwhelming, including explanations of the disease, treatments, and administrative procedures all at the same time. All families interviewed agreed on the necessity of being given information about the disease without the patient being present "so as not to worry them more". Some responses were:

> We have had to wait hours while the physician received the patient, asked a lot of questions and checked the papers we brought. Then he asked my father why he waited so long to see a doctor. Later, the nurse spoke to us about payments, appointments, and necessary tests; we waited quietly and, when the physician told my father that he had cancer, neither he nor I understood anything... (Daughter of a patient age 75 with lung cancer)

Most family members said that the words and language used by the physicians were difficult to understand – terms such as palliative treatment, cardiac toxicity, analgesic, adjuvant, chemotherapy, neoadjuvant chemotherapy, disseminated

disease, and incurable disease. They also said that it takes time to really understand the disease. They emphasized the importance of continuous communication between physicians and families to increase their knowledge and help them understand the information. They added that very useful information was gained in the waiting rooms from talking with the families of other patients.

Focus group participants asked for the availability of written information. Almost all the families had questions about the treatment process, and wanted more information about what to expect as treatment was given. They also wanted to know where they could find support or a guide to living with a patient with cancer.

> When my son had chemotherapy for testicular cancer, I made him eat some hot chicken soup. Afterwards, I felt very guilty - nobody had told me that he had an ulcerated esophagus. I made him suffer... (Mother age 40, son age 19)

All the families said that although the patients had signed "consent" papers, the patients themselves had not made the decisions about their treatment.

> I do not believe that my wife was able to decide her treatment; the doctor told her that she had breast cancer and that they would give her medicine for three months to make the tumor smaller, after that they would remove her breast...

Several relatives did not understand the concept of chronic disease and said that their worries about money increased with time. In many cases they talked about loans and asking for money from other relatives. They often spoke of the duty of the family to care for someone who was sick.

Family members were convinced of the importance of family support to patients, which explains their interest in understanding the patient's diagnosis, treatment options, and responses and/or reactions to therapy. They felt that the patient's only concern should be to be cured, while the family would take care of the monetary issues.

> Each new appointment you must be prepared for bad news and the request for a new treatment, and each time the medicines are more expensive... (Members of one of the focus group with patients' relatives)

Economic concerns and responses about the continuously escalating cost of medications explains the high number of INCan patients who participate in clinical trials, for many of them participation in the trial is the only means to obtain treatment. In Mexico, the price of many medications for cancer is out of the reach for most of the population, certainly for patients eligible for care at INCan.

11.4 Discussion

Study results provide a clear picture of the Mexican people who receive care in the public hospitals, and raise questions about the manner in which physicians explain the diagnoses, prognoses, and treatment options to patients and their families. Approximately 80 % of industry-sponsored clinical trials are conducted

in public hospitals. A diagnosis of cancer is itself very stressful and can influence the process of informed consent (Alexander 1990; Doyal and Tobias 2001). For this reason, it is necessary to better understand the factors which influence decision-making by patients and their families. There is a need to implement significant changes in the process of informing patients about their illness and its consequences, the chronic nature of cancer, the available treatment options, and what each of these imply. This study has shown that at present patients do not clearly understand these issues.

Poor communication between physicians and patients leads us to question if the patients are taking their medication in accordance with the physician's wishes. Since many INCan patients take part in clinical trials, not following the treatment regimen can distort the trial data for the treatment.

11.4.1 The Role of the Family in Decision-Making

Most INCan patients (74 %) are either unemployed or work without salary, and therefore depend heavily on their family. Consequently, relatives have a part in decision-making, almost always influenced by the economic situation of the family while trying to obtain the best care possible for the patient. In Mexican society, affection, solidarity and care are an integral part of daily family interaction.

When a family member is ill, it is common to see various relatives accompanying the patient to physician appointments. The same applies when the patient is admitted for treatment; sometimes it is difficult to differentiate the patient, as an individual, from his family. In Mexico (and other societies), the physician will confer with the family before talking to the patient. The family and the physician will frequently decide the strategy for telling the patient about the diagnosis (Chan 2004).

Any patient who receives a diagnosis of cancer experiences a sudden turning point in their life. Readjustment during the grief process includes the loss of their previous autonomy and perception of self, and eventually leads to a re-interpretation of self-identity and the recovery of individual autonomy. The loss of autonomy affects the capacity of the individual to make decisions (Calinas Correia 1998). In these circumstances, unlike the situation in other countries where patients are the primary subject by tradition and law (Moazam 2000; Younge et al. 1997), in Mexico there is a preference for decisions by the family (Fan 1997).

It is the family which most frequently questions medical decisions, complains about the small amount of information they receive, gives news to other family members, and assumes financial responsibility for the patient. During the focus groups it was clear that the relatives were concerned about the health of the patient, but their major anxiety related to money. For this reason, it is more than possible that it is the family who encourages the patient to participate in a clinical trial.

11.4.2 Who Decides?

During the interviews it was clear that the only concern of the patients was their illness and its consequences – their preoccupation with physical pain and expectation of life; none showed active interest in treatment decisions, financial arrangements, or long-term socio-economic consequences for themselves or their families.

The right to self-determination, based on respect for patient autonomy in Anglo-American applied ethics, should be adapted to the Mexican context. Public hospital physicians must remember that valid informed consent requires meeting three essential conditions – information, ability to understand, and voluntary consent (Younge et al. 1997). Physicians must keep in mind the socio-economic circumstances of the INCan patients and their families (little formal education and poverty), and be sure that the patients have understood the information and explanations they have been given (Clará et al 2004). Otherwise, one of the essential factors for valid informed consent is missing. Few physicians remember that most of their patients have a limited understanding, or recall only a fraction of the information they have received (Parker 2000), including instructions about how to take medication.

When asking for informed consent for clinical trials, more time could be given to ensure that the information has been understood. The complexity of the information provided by the health personnel and the poverty of the population treated in public medical centers leads patients to consent in order to access free treatment and better care.

Health services cannot be separate from cultural and sociopolitical norms (Nutbeam 2000), which, in Mexico, include the role of the family in making decisions. The paradigm of autonomy, which in many societies has superseded the paradigm of social context (Schäfer et al. 2006), may not be the best for the Mexican population. We feel that the administrators of the health institutions of Mexico (and possibly other countries in the region) must recognize the difficulties patients have in understanding a clinical environment and providers with a health-illness paradigm, and develop ways to improve doctor-patient communication. It is necessary to study further the role of families in the decision-making process.

Acknowledgment This chapter was prepared by the Mexican NGO Gestión Social para el Desarrollo (Social Management for Development – GESOC, http://www.gesoc.org.mx/quienes_somos.html) as part of the project "Advocacy for Informed Consent in Mexico". GESOC investigates, monitors, and evaluates the performance of public institutions, non-governmental organizations, and companies with a major public impact. This study was funded by the Young Leaders Scholarship of the World Bank. The authors thank the patients and families who participated in the study, Rita Vaca and María Elena Hernández of the Social Services Department of the National Cancer Institute of Mexico (INCan) for their cooperation, and Dr. Laura Suchil and Dr. Alejandro Mohar, Executive Director of INCan, for their support.

References

Alexander, M. 1990. Informed consent, psychological stress and noncompliance. *Human Medicine* 6(2): 113–119.

American Medical Association. 2008. Informed consent. http://www.ama-assn.org/ama/pub/category/4608.html. Accessed 22 July 2008.

Beauchamp, T.L., and J.F. Childress. 2009. *Principles of biomedical ethics*. New York: Oxford University Press.

Blackhall, L., G. Frank, S.T. Murphy, et al. 2001. Bioethics in a different tongue: The case of truth-telling. *Journal of Urban Health* 78: 59–71.

Blackhall, L.J., S.T. Murphy, G. Frank, et al. 2002. Ethnicity and attitudes toward patient autonomy. In *Healthcare ethics and human values: An introductory text with readings and case studies*, ed. W.M. Fulford, D. Dickerson, and T. Murray, 187–192. Hoboken: Wiley.

Calinas Correia, J. 1998. On autonomy and identity. *Journal of Medical Ethics* 24: 414–415.

Chan, H.M. 2004. Informed consent Hong Kong style: An instance of moderate familism. *The Journal of Medicine and Philosophy* 29(2): 195–206.

Clará, A., B. Román, and F. Vidal-Barraquer. 2004. A practical approach to ethical problems in surgical emergencies. *Acta Chirurgica Belgica* 104: 125–128.

College of Physicians and Surgeons of Alberta. 2002. Competency assessment and surrogate decision making: Responsibilities and roles of a physician. Alberta (Canada). http://www.cpsa.ab.ca/Libraries/Res_Messenger/m099.pdf. Accessed 1 Nov 2012.

Doyal, L., and J.S. Tobias. 2001. *Informed consent in medical research*, 334–344. London: BMJ Books.

Fan, R. 1997. Self-determination vs. Family-determination: Two incommensurable principles of autonomy: A report from East Asia. *Bioethics* 11(3-4): 309–332.

Grubb, A., R. Scott, P. Lewis, et al. 2003. Law relating to consent. In *Manual for research ethics committees*, ed. Sue Eckstein, 59–84. Cambridge: Cambridge University Press.

Kagawa-Singer, M. 1996. Cultural systems related to cancer. In *Cancer nursing: A comprehensive textbook*, ed. S.B. Baird, R. McCorkle, and M. Grant, 38. Philadelphia: Elsevier/W.B. Saunders Company.

Kipendorff, K. 2004. *Content analysis: An introduction to its methodology*. Thousand Oaks: Sage.

Kleinman, A., L. Eisenberg, and B. Good. 1978. Culture, illness and care: Clinical lessons from anthropologic and cross-cultural research. *Annals of Internal Medicine* 88(2): 251–258.

Merton, R., M. Fisk, and P. Kendall. 1956. *The focused interview: A report of the Bureau of Applied Social Research*. New York: Columbia University Press.

Moazam, F. 2000. Families, patients and physicians in medical decision making: A Pakistani perspective. *The Hastings Center Report* 30: 28–37.

Nutbeam, D. 2000. Health literacy as a public health goal: A challenge for contemporary health education and communication strategies into the 21st century. *Health Promotion International* 15(3): 259–267.

Parker, R. 2000. Health literacy: A challenge for American patients and their health care providers. *Health Promotion International* 15(4): 277–283.

Schäfer, P.C., K. Putnik, B. Dietl, et al. 2006. Medical decision-making of the patient in the context of the family: Results of a survey. *Supportive Care in Cancer* 14(9): 952–959.

Secretaría de Salud. 2001. Hogares con gastos catastróficos por motivos de salud (Households affected by catastrophic health events). México DF: Secretaría de Salud.

Secretaría de Salud. 2007. Ley General de Salud, Artículo 77 bis 37 (General Health Act article 77 bis 37). México DF: Secretaría de Salud.

Young, R. 2001. Informed consent and patient autonomy. In *A companion to bioethics*, ed. H. Kuhse and P. Singer, 441–455. Oxford: Wiley.

Younge, D., P. Moreau, A. Ezzat, and A. Gray. 1997. Communicating with cancer patients in Saudi Arabia. *Annals of the New York Academy of Sciences* 09: 309–316.

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

Gabriela E. Minaya-Martínez, Susy Y. Olave-Quispe, and Duilio J. Fuentes-Delgado

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

G.E. Minaya-Martínez (✉) • D.J. Fuentes-Delgado
La Oficina General de Investigación y Transferencia Tecnológica (OGITT), Instituto Nacional de Salud of Perú, Lima, Peru
e-mail: gminayam@gmail.com

S.Y. Olave-Quispe
Unit of Executive Support, División de asuntos internacionales y de la Unión Europea, Agencia Española de Medicamentos y Productos Sanitarios, Madrid, Spain

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

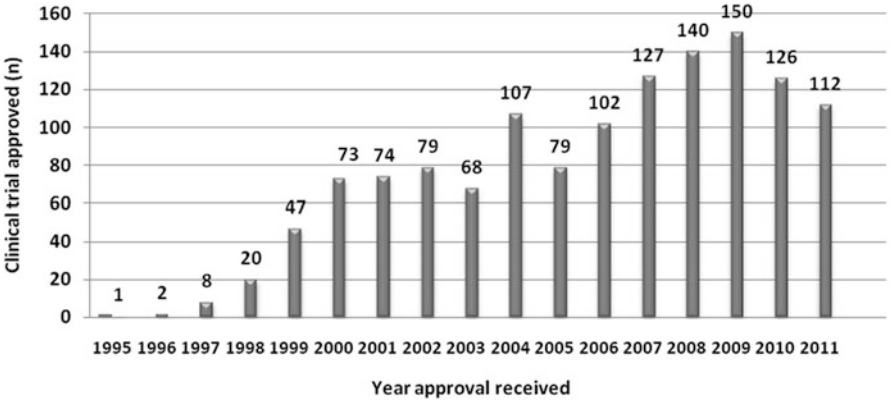

Fig. 12.1 Number of clinical trials approved by the Ministry of Health: Peru, 1995–2011 (Source: For 1995–2002 Database of the Department of Health. For 2003–2011 Database and Archives of Clinical Trials of the General Office of Research and Technology Transfer (OGITT). National Institute of Health (INS))

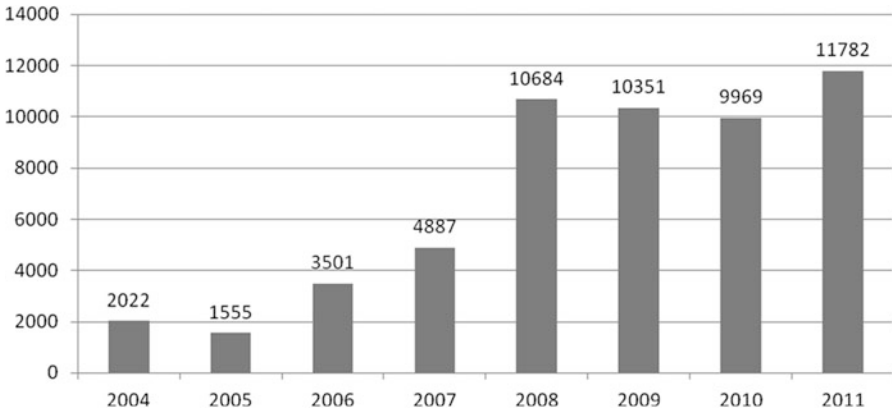

Fig. 12.2 Growth in the number of clinical trial participants in Peru: 2004–2011 (Source: Database and Archives of Clinical Trials of the General Office of Research and Technology Transfer (OGITT). National Institute of Health (INS))

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

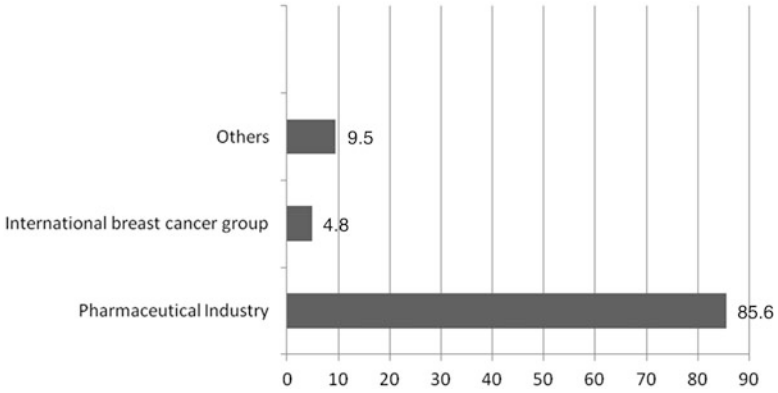

Fig. 12.3 Clinical trials by sponsor, Peru: 2004–2010 (Source: Database and Archives of Clinical Trials of the General Office of Research and Technology Transfer (OGITT). National Institute of Health (INS))

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

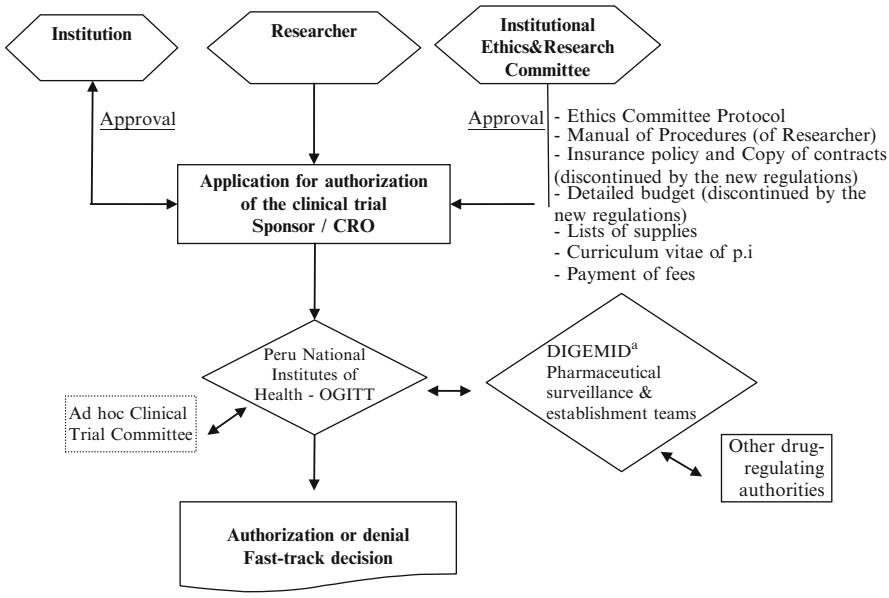

Fig. 12.4 Administrative process for the authorization of a clinical trial, 2006 ([a]Dirección General de Medicamentos, Insumos y Drogas (DIGEMID). Ministry of Health. www.digemid.minsa.gob.pe/)

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.

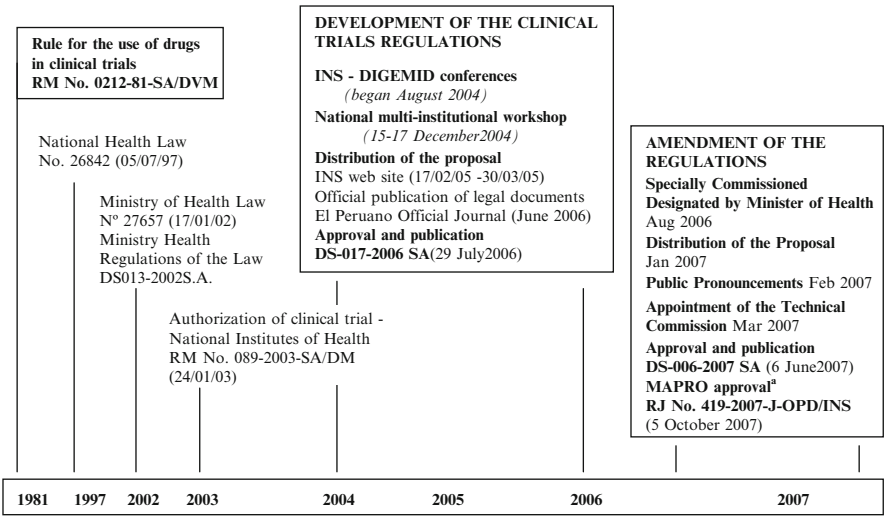

Fig. 12.5 Significant dates of the clinical trial legislation process in Peru ([a]*Handbook of Administrative Procedures* (Manual de Procedimientos Administrativos))

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.

References

Abbott, L., and C. Grady. 2011. A systematic review of the empirical literature evaluating IRBs: What we know and what we still need to learn. *Journal of Empirical Research on Human Research Ethics* 6(1): 3–19. doi:10.1525/jer.2011.6.1.3.

Agostine, R.A., D. Bhagnianadh, C. Bontempo, et al. 2011. *Putting contract research organizations on the radar*. Amsterdam: SOMO.

Asociacion Médica Peruana (AMP). 2007a. Press release 12 Sept. http://www.asociacionmedicaperuana.org/notas_deprensa.htm. Accessed 15 July 2007, not available at present.

Asociación Médica Peruana (AMP). 2007b. Press release 14 May. http://www.asociacionmedicaperuana.org/notas_deprensa.htm. Accessed 15 July 2007, not available at present.

Bodenheimer, T. 2000. Clinical investigators and the pharmaceutical industry. *The New England Journal of Medicine* 342(20): 1539–1544.

Brown, J.G. 1998. Institutional review boards: Their role in reviewing approved research. Department of Health and Human Subjects. Office of the Inspector General. June OEI 01-97-00190. http://oig.hhs.gov/oei/reports/oei-01-97-00190.pdf. Accessed 3 Sept 2012.

Burris, S., and K.U.S. Moss. 2006. Health researchers review their ethics review boards: A qualitative study. *Journal of Empirical Research on Human Research Ethics* 1(2): 39–58.

Council for International Organizations of Medical Sciences (CIOMS), World Health Organization (WHO). 2002a. International ethical guidelines for biomedical research involving human subjects, Geneva. http://www.cioms.ch/publications/guidelines/guidelines_nov_2002_blurb.htm. Accessed 15 June 2011.

Council for International Organizations of Medical Sciences (CIOMS), World Health Organization (WHO). 2002b. International ethical guidelines for biomedical research involving human subjects. Geneva see guideline 13: Research involving vulnerable persons, 65. http://www.cioms.ch/publications/guidelines/guidelines_nov_2002_blurb.htm. Accessed 2 Nov 2012.

Diario La República. 2007. ¿Ensayos clínicos inseguros? (Unsafe clinical trials?). Press release 15 May. http://www.larepublica.pe/15-05-2007/ensayos-clinicos-inseguros. Accessed 2 Nov 2012.

Diario Perú 21. 2007. Menos control en experimentos con seres humanos (Less control of experiments involving humans). Press release 3 Feb. http://peru21.pe/noticia/12674/menos-control-experimentos-seres-humanos. Accessed 2 Nov 2012.

Editorial. 2011. Who watches the watchmen? *Nature* 476: 125.

Elliot, C. 2010a. What happens when profit margins drive clinical research? Mother Jones, September/October. http://motherjones.com/environment/2010/09/clinical-trials-contact-research-organizations. Accessed 2 Nov 2012.

Elliot, C. 2010b. Poor reviews. Mother Jones, September/October. http://motherjones.com/print/71816. Accessed 26 Oct 2012.

Elliot, C. 2011. Useless pharmaceutical studies. Real harm. *New York Times*, 28 July. http://www.nytimes.com/2011/07/29/opinion/useless-pharmaceutical-studies-real-harm.html?_r=1&emc=tnt&tntemail0=y. Accessed 26 Oct 2012.

Fuentes, D. Ensayos Clínicos en el Perú (1995–2006). [Tesis para optar al título de Especialista en Medicina Interna]. Lima: Facultad de Medicina, Universidad Nacional Mayor de San Marcos; 2008.

Fuentes-Delgado, D. 2007. Ensayos clínicos en el Perú 1995–2006 (Clinical trials in Peru 1995–2006). Thesis, Universidad Nacional Mayor de San Marcos, Lima.

Fuentes, D., and D. Revilla. 2007. Acreditación de Comités de Ética en Investigación, como parte de un proceso (Accreditation of research ethics committees, as part of the process). *Anales de la Facultad de Medicina Lima* 68(1): 67–74.

Fuentes, D., and G. Minaya. 2009. ¿Cuánto puede avanzar la ciencia y la tecnología médica en un periodo de seis meses en el Perú? (How much can medical science and technology advance during six months in Peru?). *Revista Brasileira de Bioética* 5(1–4): 34–47.

Garrafa, V., and C. Lorenzo. 2008. Moral Imperialism and multi-centric clinical trials in peripheral countries. *Cad Saúde Pública* (Rio de Janeiro) 24(10): 2219–2226. http://www.scielo.br/pdf/csp/v24n10/03.pdf. Accessed 26 Oct 2012.

Hoyos Vásquez, G., and O.C. Maldonado de Delgado. 2012. El Instituto de Bioética de la Pontificia Universidad Javeriana y sus Programas de Maestría y Especialización en Bioética (The Bioethics Institute at the Universidad Javeriana and its graduate programs in bioethics). In La Educación en Bioética en América Latina y el Caribe**:** experiencias realizadas y desafíos futuros (Education in bioethics in Latin America and the Caribbean. Past experiences and future challenges), ed. S.M. Vidal, 329–342. Montevideo: UNESCO.

Instituto Nacional de Estadísticas e Informática (INEI). 2004–2006. Encuesta Nacional de Hogares (National Institute of Statistics and Informatics – National Household Survey). http://www.inei.gob.pe/. Accessed 15 Mar 2010.

Instituto Nacional de Estadísticas e Informática (INEI). 2007. Información social (National Institute of Statistics and Informatics Social information). http://www.inei.gob.pe/. Accessed 15 Mar 2010.

Instituto Nacional de Estadísticas e Informática (INEI). 2008. Encuesta Demográfica y de Salud Familiar (National Institute of Statistics and Informatics – Demographic and family health survey). http://www.inei.gob.pe/. Accessed 20 Mar 2010.

Instituto Nacional de Salud (INS). 2006. Resolución Directoral Nº 177-2006-J-OPD/INS (National Institute of Health Director's Resolution Nº 177-2006-J-OPD/INS)

Instituto Nacional de Salud (INS). 2007. Manual de Procedimientos Versión 01 (Manual of Procedures, Version 1). http://www.ins.gob.pe/repositorioaps/0/2/jer/ens_ins3/MANUAL_DE_PROCEDIMIENTOS.pdf. Accessed 26 Oct 2012.

Instituto Nacional de Salud (INS). 2009. Perspectivas de Regulación sobre ensayos clínicos en Peru, Lima. http://www.ins.gob.pe/ensayosclinicos/reporteador/Perspectivas_Regulacion_Ensayos_Clinicos_Peru_2009.pdf. Accessed 15 June 2010.

Instituto Nacional de Salud (INS). 2012. Estadísticas de los Ensayos Clínicos (National Institute of Health Clinical trial statistics). http://www.ins.gob.pe/portal/jerarquia/2/829/estadisticas-de-los-ensayos-clinicos/jer.829. Accessed 26 Oct 2012.

International Conference of Harmonization of Technical Requirement for Registration of Pharmaceuticals for Human Use (ICH). 1996. *Good clinical practices: Consolidated guidance E6 (R1)*. Geneva: ICH Secretarial.

Kottow, M.H. 2005. Conflictos en ética de investigación con seres humanos (Conflicts in human research ethics). *Cadernos de Saúde Pública* 21(3): 862–869.

Lecca-García, L., F. Llanos-Zavalaga, and Y. Jorge Erika. 2005. Características de los Comités de Ética en Investigación del Perú autorizados para aprobar ensayos clínicos (Characteristics of Peruvian research ethics committees that have authorized to approve clinical trials to be conducted in Peru). *Revista Médica Herediana* 16(1): 3–10.

Lemmens, T., and B. Freedman. 2000. Ethics review for sale? Conflict of interest and commercial research review boards. *The Milbank Quarterly* 78: 547–584.

Minaya-Martínez, G., and R. Díaz-Sandoval. 2008. Capacidad de evaluación de los ensayos clínicos por los comités de ética (Competency of ethics committees to evaluate clinical trials). *Revista de la Sociedad Peruana de Medicina Interna* 21(4): 153–165.

Ministerio de Salud. 1981. Normas para el Uso de Drogas en Ensayos Clínicos Resolución Ministerial Nº 0212-81-SA/DVM (Rules for the use of medicines in clinical trials. Ministerial Resolution Nº 0212-81-SA/DVM). El Peruano, Diario Oficial.

Ministerio de Salud. 2003. Disponen que proceso administrativo establecido en el TUPA del Ministerio sea competencia del Instituto Nacional de Salud. Resolución Ministerial Nº 089-2003-SA/DM (The administrative process established in the TUPA of the Ministry of Health will be transferred to the National Institute of Health. Ministerial Resolution Nº 089-2003-SA/DM). El Peruano, Diario Oficial.

Ministerio de Salud. 2007a. Disponen que la Oficina General de Comunicaciones publique en el portal de internet el proyecto modificatorio del Reglamento de Ensayos Clínicos Resolución Ministerial Nº 057-2007 16 de enero (It has been decided that the General Communication Office should post in the webpage the proposal to modify the clinical trial regulation of the Ministry of Health Nº 057-2007, Jan 16).

Ministerio de Salud. 2007b. Conforman Comisión Técnica que analizara sugerencias o recomendaciones al proyecto de Modificación del Reglamento de Ensayos Clínicos. Resolución Ministerial Nº 164-2007/MINSA del 23 de febrero (The members of the technical committee that will analyze the suggestions and recommendations to the proposal to modify the regulation of clinical trials have been selected. Resolution of the Ministry of Health Nº 164-2007/MINSA, 23 February). El Peruano, Diario Oficial.

Ministerio de Salud. 2007c. Amplían conformación de Comisión técnica encargada de analizar sugerencias o recomendaciones recibidas respecto del proyecto de Modificación del Reglamento de Ensayos Clínicos. Resolución Ministerial Nº 225-2007/MINSA del 19 de marzo (Members are added to the technical committee that will analyze the suggestions and recommendations to the proposal to modify the regulation of clinical trials. Resolution of the Ministry of Health Nº 225-2007/MINSA, 19 March). El Peruano, Diario Oficial.

Ministerio de Salud (MINSA). 2012. Estadísticas e Indicadores (Ministry of Health – Statistics and Indicators). http://www.minsa.gob.pe/portada/estadistica.htm. Accessed 26 Oct 2012.

Olave-Quispe, S. 2007. Outsourcing clinical trials to Latin America: Trends and risks. In: Clinical trials and protection of trial subjects in low-income and developing countries. Expert meeting organized by The Netherlands Wemos Foundation, at the European Parliament, Brussels, 6 Nov 2007.

Olave-Quispe, S. 2011. Elaboración y validación de una guía de evaluación de los aspectos Ético-científicos de los EC para uso de los CEI de Perú (Making and validating a guide to be used by ethics committees during the evaluation of scientific and ethical aspects of study protocols). Dissertation, Universidad de Sevilla, Spain.

Olave-Quispe, S., D. Fuentes-Delgado, G. Minaya-Martínez, et al. 2012. The development and validation of a guide for Peruvian research ethics committees to assist in the review of ethical-scientific aspects of clinical trials. In *Human medical research: Ethical, legal and socio-cultural aspects*, ed. Jan Schildmann, Verena Sandow, Oliver Rauprich, and Jochen Vollmann, 97–116. Heidelberg: Springer.

Pfeiffer, M.L., and L.F. Belli. 2012. Antecedentes y realidad de la educación en bioética en Argentina (History and reality of bioethical education in Argentina). In La Educación en Bioética en América Latina y el Caribe: experiencias realizadas y desafíos futuros (Education in bioethics in Latin America and the Caribbean. Past experiences and future challenges), ed. S.M. Vidal, 195–218. Montevideo: UNESCO.

Prescrire. 2007. Vigilance. *Rev Prescrire* 27(282): 244.

Prescrire Editorial Staff. 2010. ICH: An exclusive club of drug regulatory agencies and drug companies imposing its rules on the rest of the world. *Rev Prescrire* 30(317): 222–225.

Prescrire. 2011. Medicines agencies too often under the influence of drug companies. *Prescrire International* 20(115): 108.

Presidente de la República de Perú. 1992. Reglamento de Organización y Funciones del Ministerio de Salud. Decreto Supremo Nº 002-002-92-SA, Artículo 74 (Regulation of the organizational and functional structure of the Peruvian Ministry of Health. Supreme Decree Nº 002-002-92-SA, Article 74). El Peruano, Diario Oficial.

Presidente de la República de Perú. 2002. Reglamento de la Ley del MINSA. Artículo 11. Órgano de Línea o central del MINSA. Encargado del Control de Medicamentos, Insumos y Drogas; con el objetivo funcional general de poner al alcance de la población productos farmacéuticos y afines, de calidad, seguros y eficaces, y promocionar el uso racional de medicamentos (Regulation of the Ministry of Health's Act. Supreme Decree Nº 013-2002-SA. Article 11. Subordinate or central unit of the Ministry of Health Responsible for the control of pharmaceuticals, supplies and drugs, aimed at ensuring that the population has access to quality pharmaceuticals, that are safe and effective, and at promoting the appropriate use of pharmaceuticals). El Peruano, Diario Oficial.

Presidente de la República de Perú. 2006. Reglamento de Ensayos Clínicos en el Perú. Decreto Supremo Nº 017-2006-SA del 26 de julio (Regulation of clinical trial. Supreme Decree Nº 017-2006-SA, 16 July). El Peruano, Diario Oficial.

Presidente de la República de Perú. 2007. Modifican el Reglamento de Ensayos Clínicos en el Perú. Decreto Supremo Nº 006-2007-SA (Changes to the regulation of clinical trials in Peru. Supreme Decree Nº 006-2007-SA). El Peruano, Diario Oficial.

Silverman, E. 2010. Why clinical trials are becoming more expensive. *Pharmalot*. http://www.pharmalot.com/2010/05/why-clinical-trials-are-becoming-more-expensive/. Accessed 3 June 2012.

Tealdi, J.C. 2003. Ética de la investigación: el principio y el fin de la bioética (Research ethics: The beginning and end of bioethics). *Summa Bioética Mexico* 1: 69–72.

Tealdi, J.C. 2004. La bioética latinoamericana: ¿ante un nuevo orden moral? (The Latin-American bioethics: Is it facing a new moral order?). In Bioética: ¿estrategia de dominación para América Latina? (Bioethics: Strategy for domination of Latin America?). ed. M.L. Pfeiffer, 43–58. Buenos Aires: Ediciones Suárez Press.

Tealdi, J.C. 2006. Historia y significado de las normas éticas internacionales sobre investigaciones biomédicas (History and meaning of international ethical norms regarding bioclinical research). In *Investigación en seres humanos y políticas de salud pública*, eds. G. Keyeux, V. Penchaszadeh, and A. Saada, 33–62. Bogota: Universidad Nacional de Colombia/Red Latino-Americana y del Caribe de Bioética de UNESCO.

Tealdi, J.C. 2010. Bioética de los derechos humanos. Investigaciones biomédicas y dignidad humana (Bioethics of human rights. Bioethical research and human dignity). Instituto de Investigaciones Jurídicas de la UNAM: México. http://ciedbiblioteca.blogspot.com/2010/08/bioetica-de-los-derechos-humanos.html. Accessed 26 Oct 2012.

Tufts University. 2010. Rising clinical trial complexity continues to vex drug developers. http://csdd.tufts.edu/news/complete_story/pr_ir_may-jun_2010. Accessed 3 June 2012.

Ugalde, A., and N. Homedes. 2011. Cuatro palabras sobre ensayos clínicos: ciencia/negocio, riesgo/beneficio (Four words regarding clinical trials: Science/profit, risks/benefits). *Salud Colectiva Buenos Aires* 7(2): 133–146.

United Nations Educational, Scientific and Cultural Organization (UNESCO). 2005. Declaration on Bioethics and Human Rights. http://unesdoc.unesco.org/images/0014/001461/146180S.pdf. Accessed 15 June 2011.

Vidal, S. 2009. Hacia un sistema regional de evaluación ética de investigaciones en salud (Towards a regional system of ethical evaluation of biomedical research). In Peligros y riesgos en las investigaciones (Bio) Ética en la investigación seres vivos (Dangers and risks in bioethical research with humans), eds. S. Ceccheto, M.L. Pfeiffer, and A. Estévez (comp.), 187–206. Buenos Aires: Antropofagia Press.

Whitney, S.N., K. Alcser, C. Schneider, et al. 2008. Principal investigator views of the IRB system. *International Journal of Medical Sciences* 5(2): 68–72.

World Health Organization (WHO). 2007. Data and statistics. http://www.who.int/research/es/. Accessed 15 Mar 2010.

World Population Data. 2009. http://www.prb.org/pdf09/09wpds_sp.pdf. Accessed 15 Mar 2010.

Chapter 13
Conclusion

Antonio Ugalde and Nuria Homedes

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

A. Ugalde
Department of Sociology, University of Texas, Austin, TX, USA

N. Homedes (✉)
School of Public Health, Division of Management Policy and Community Health, University of Texas Houston Health Science Center, El Paso, TX, USA
e-mail: nhomedes@utep.edu

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_13,

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.

Index

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,