Chapter 3
Globalization and Clinical Research in Latin America

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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.

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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.

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