Chapter 7
Progress and Challenges of Clinical Research with New Medications in Brazil

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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,

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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.

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