Chapter 6
Brazil: The System for the Protection of Voluntary Participants in Research

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6.1 First Steps in Research Involving Humans

Discussions on the establishment of ethical parameters and the regulation of clinical trials with human participants began in Europe and the United States in the 1950s, gaining increasing emphasis during the 1970s and 1980s. In Brazil, clinical research grew during the 1980s, when investigators from Europe and the USA invited major Brazilian centers – public hospitals and academic centers – to take part in clinical trials. As a result, the first centers for research were established, and, as in other parts of the world, some incidents happened which caused concern and illustrated the need for regulations to protect study subjects. The Norplant study was a major case in point.

Norplant, a long-term (five years) contraceptive, developed by the Population Council of the United States, consists of six capsules of levonorgestrel inserted beneath the skin (Israel and Dacach 1993). Norplant began to be used in Brazil in the mid-1970s, but was not reviewed by the health authorities until 1984. At that time the country had a military government, many universities had links with population centers, and ethical standards were lowered. For example, when the University of Campinas presented the Norplant project to the health authorities in 1984, the President of the University was a member of the advisory committee of the Population Council, and the study was approved without fulfilling fundamental ethical standards. The study did not require women to give informed consent, the

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use of the product was illegally promoted in the mass media, the number of recruitment centers grew from seven to 21 without previous authorization, and the number of women recruited in the study was also greater than the approved sample. Between August 1984 and January 1986, 3,562 mostly poor women were recruited into the study when permission had been given for only 2,000 study participants. Additionally, although it had been presented to the health authorities as a Phase III study, the 1984 annual report of the Population Council stated that it was a clinical trial to promote Norplant (Dos Reis 1990).

With the return of a democratic government, feminists demanded a review of birth control programs in Brazil, which led to the formation of a Commission for the Study of Women's Reproductive Rights in the Ministry of Health. Following the review of two Norplant studies, one in Rio de Janeiro (Koifman report) and the other in Campinas – Fortaleza and Curitiba (Hardy report), which documented the occurrence of the ethical abuses mentioned above and the emergence of adverse events that remained unattended, the authorization to conduct clinical trials with Norplant was cancelled on January 22, 1986.

The 1988 reform of the Brazilian Constitution strengthened the National Health Council (Conselho Nacional de Saúde – CNS), composed of representatives of users, agencies, and health care workers, with the objective of increasing social control and community participation in health sector management. These events had international repercussions (Vieira and Hossne 1987), the CNS prioritized the regulation of research involving humans and in 1988 approved Resolution Number 1. This resolution included the first standards for health research and discussed the need to form research ethics committees. For its part, the agency responsible for health surveillance and for authorizing the importation of medications for clinical trials released its Manual of Procedures, which included a Risk Recognition Form, as a way of self-protection against possible accusations from study participants (or their families) who felt they had been harmed by participating in clinical trials of products not approved for use in humans.

As Brazilian researchers were included in international trials, the CNS, especially its Committee on Science and Technology (CICT), was confronted with ethical questions, which had not been foreseen in the first resolution. For example, the military had conducted secret experiments, there were internationally supported studies that had not been approved in the country of origin, and studies had taken place in accredited Centers of Excellence where the level of risk to participants was so high that it was said that study subjects had become human guinea pigs. There is evidence that healthy soldiers were exposed to Leishmaniasis to test the effectiveness of a new treatment; also, contrary to Brazilian therapeutic guidelines, AIDS patients included in the control group of one clinical trial were denied triple antiretroviral treatment.

Seven years after the first Resolution, a study confirmed the need to modify and strengthen the protections for human research participants. Few ethics committees had been formed, the scientific community did not recognize the ethical standards, and society in general was totally uninformed. There had

been important problems in the implementation of the regulation; for example, there were no strategies to form ethics committees or training programs to help them understand and execute their functions (Francisconi et al 1995). The responsibilities of the researchers and those of the CICT were not clearly separated; for example, the system allowed accredited centers that had been supervised during the implementation of a clinical trial to conduct, during a specified period, other research projects – regardless of their design and complexity- without notifying the CICT.

6.2 Engaging Communities in the First Revision of the Regulations

The premises governing this revision of the regulations were as follows:

1. The regulations will apply to all establishments and investigators conducting research involving human beings, no matter in which area of knowledge gains are sought, and they will not be limited to the research conducted in health centers and hospitals. This important change was based on the premises that the amount of science and technology research would increase, and that any project involving human subjects holds risks and uncertainties which cannot always be foreseen or prevented, but which may affect the health of study participants (Hossne 2003). At that time, health was considered not to be merely the absence of disease, but the balance between individuals and their environments, and it involved aspects of physical, psychological, and social wellbeing
2. The regulations will be based on updated ethical principles
3. The final product will reflect Brazilian culture and ideas, which will be unveiled through consultations and meetings for community input

This was the first time that Brazilian decision-makers sought the involvement of communities and experts, and engaged in a wide consultation process. The first step was to identify the organizations and people to get involved. It was decided to include, among others, researchers and administrators of facilities conducting research with human subjects, experts in the analysis of bioethics in public policy, scientific associations, universities, research centers, professional associations, human-rights groups, experts in health law, consumer advocacy groups, women's movements, disease-oriented associations (i.e., diabetes association, AIDS-patients groups, etc.), and religious institutions. In addition, other experts were invited to guide the group in addressing ethical dilemmas, such as research involving human reproduction, genetics, bio-security, indigenous populations, new medications and vaccines, and new devices and equipment for the diagnosis and treatment of health problems.

Understanding the social repercussions and the multidisciplinary nature of protecting human research participants, the CNS delegated responsibility for updating the existing regulations to a multidisciplinary working group with representatives from all interest groups.[1]

The members of the coordinating group were responsible for engaging other members of their agencies and organizations in the discussion and in the various scientific events that were organized around the general theme of bioethics in clinical research. Box 6.1 lists the principal strategies used in this process. After a thorough review of international codes and national regulations, a first draft of the new regulatory framework was produced and 2,300 copies were mailed along with letters soliciting comments and suggestions to incorporate in the new regulation.

To encourage participation and to include the opinions of other groups, information about the project was published in the National Medical Council's journal, Bioética (CFM), as well as in 20,000 copies of the National Health Service epidemiological newsletter. The Tenth National Conference on Health included a session on this subject, and other scientific organizations, professional and non-professional associations, and universities held seminars to facilitate the interchange of ideas. Several institutions established work groups and submitted documents explaining their position and suggestions, and the press and other media produced articles and reported on the progress and challenges of this great social movement.

[1] Participants included the National Medical Council (Conselho Federal de Medicina – CFM), the National Feminist Network for Reproductive Health and Rights (Rede Nacional Feminista de Saúde e Direitos Reprodutivos – REDE), the Brazilian Bar Association (Ordem dos Advogados do Brasil – OAB), the Brazilian Bishops Conference (Conselho Nacional dos Bispos do Brasil – CNBB), the Society of Theology and Religious Sciences (Sociedade de Teologia e Ciências da Religião – SOTER), the Brazilian Association of Medical and Dental Device Manufacturers (Associação Brasileira da Indústria de Equipamentos Médico- Odontológicos – ABIMO), the Brazilian Society of Biomedical Engineering (Sociedade Brasileira de Engenharia Biomédica – SBEB), the pharmaceutical section of the National Confederation of Industry (Confederação Nacional da Indústria – CNI), the National Research Institute, Ministry of Science and Technology (Conselho Nacional de Desenvolvimento Científico e Tecnológico do Ministério de Ciência e Tecnologia – CNPqMCT), the Department of Coordination of Scientific and Technology Development of the Ministry of Health (Coordenação de Desenvolvimento Cientifico e Tecnológico do Ministério da Saúde – DECITMS), the National System of Sanitary Surveillance, Ministry of Health (Secretaria de Vigilância Sanitária, Ministério da Saúde – SNVS), consumer representatives of the Brazilian National Health System (Usuarios del Sistema Único de Salud – SUS), representatives of disease-specific non-governmental organizations (ONGs), and researchers from Fiocruz (Oswaldo Cruz Foundation) – the research agency based in the Ministry of Health.

Box 6.1: Method Used to Develop Regulations to Incorporate Ethics Principles in Research Involving Human Subjects

- Frequent discussions with the scientific community and the general population about the existing guidelines, and inviting suggestions for their improvement
- Circulation of the current international guidelines for biomedical research
- Incentives for institutional seminars for in-depth discussions on the subject
- Seminars for representatives of non-profit organizations with interest in specific diseases, and other groups of clients of the national health system
- Consolidation of the proposals and suggestions
- Presentation of a draft document of the new regulations in a public meeting
- Presentation of the draft proposals for the new standards at the Brazilian Congress of Bioethics
- Presentation and approval of the final version of the regulations at the CNS and the 10th National Health Conference

After analyzing all the documents, reports, suggestions offered in writing and during community meetings and scientific events, the Coordinating Group produced a draft document and invited the comments and suggestions from experts and organizations. This document was also presented in a public meeting, where various interest groups and national agencies had the opportunity to critique it and share their thoughts and ideas.

It should be acknowledged that the HIV/AIDS organizations played an important role during this whole process. They were well organized, and challenged the authorities for granting permission for a study involving Indinavir that violated basic ethical principles. In this study, some participants could only use one medication, and they did not have access to the results of their blood tests, which are necessary to monitor the treatment and evaluate the course of the disease. Eventually, the National Commission terminated this study in Brazil.

In this manner, through cooperation between the general population and the government, a new set of regulations were developed and organized community groups would be responsible for overseeing scientific research. In other words, scientific research was placed under social control. Society in general would ensure adherence to resolution CNS 196/96 entitled Guidelines and Norms Regulating Research Involving Human Subjects (Diretrizes e Normas Regulamentadoras de Pesquisas Envolvendo Seres Humanos) (Ministerio de

Saude 2006),[2] which is still in effect. In the case of clinical trials with especially regulated products, a system of coordination would be established with the National Agency of Sanitary Surveillance (ANVISA), established on January 26, 1999 through Law 9.782.

6.3 Resolution CNS 196, 1996: Guidelines and Norms Regulating Research Involving Human Subjects, and Supplementary Standards

Resolution CNS 196/96 established the ethical requirements and scientific fundamentals to guarantee the rights of human subjects taking part in clinical studies. It recognized that any research with humans carries risks, physical or psychological, individual or collective, making it necessary to design control mechanisms to preserve the health (physical, mental, or social) of those involved. According to the resolution, any study involving human subjects must be approved by an institutional Committee for Research Ethics (in Portuguese, Comitê de Ética em Pesquisa – CEP), composed of members without any conflict of interest with the researcher or the sponsor; and while the principal investigator bears the primary responsibility for respecting the ethical principles and submitting the protocol for review, the ethics committee is also responsible for ensuring that the study is conducted in an ethical manner.

This Resolution also created the National Commission for Research Ethics (Comissão Nacional de Ética em Pesquisa – CONEP), which is the national entity responsible for coordinating and supervising the entire system. CONEP is accountable for enforcing the norms and resolutions of the National Health Council (CNS) and has regulatory, advisory, and training functions. Several study types – including multi-center clinical trials – require CONEP to analyze the research protocols approved by a CEP. CONEP can either ratify or question the CEP's decision and when the disagreements are not resolved, CONEP's opinion is binding for all research centers in the country involved in the study. The composition of the CEPs and CONEP is multidisciplinary, and includes experts on research, bioethics, law, health, social sciences, community representatives, as well as clients of the institution where the research takes place.

The CNS 196/96 Resolution has nine chapters (Conselho Nacional de Saude 2000). The first chapter, the Preamble or Introduction, discusses the regulations in the context of constitutional and civil law; the second chapter gives definitions; the

[2] Members of the executive group responsible for Resolution 196/66: William Saad Hossne (Coordinator), Sérgio Ibiapina Ferreira Costa, Artur Custódio Moreira de Souza, Fátima Oliveira, Leocir Pessini, Simone Nogueira, Jorge Bermudez, Márcio Fabri dos Anjos, Marília Bernardes Marques, Álvaro Antonio da Silva Ferreira, Antonio Fernando Infantosi, Albanita Viana de Oliveira, Omilton Viscondi; Executive Secretary: Corina Bontempo de Freitas.

third describes ethical issues in research involving humans; the fourth discusses the characteristics of freely given and informed consent; and the fifth discusses the benefits and risks of study participation. Chapters 6, 7, 8, and 9 refer to setting up and conducting the study, including the flow diagram for project approval and the distribution of responsibilities among the different participants and institutions.

The ethical guidelines emphasize compliance with the fundamental standards listed in Box 6.2, which are based on universally accepted bioethical principles (Hossne 2006). Bioethics is rooted in classical ethics together with the more recent theories of Kant, and of human rights, described by Beauchamp and Childress (2008). Included also, are ethics of responsibility, of caring, of the plurality of moral perspectives, and Latin American values of solidarity, equity, and collective health.

Box 6.2: Ethical Standards for Research Involving Human Subjects

- The study should be of sufficient scientific quality and should be based on any previous animal or laboratory studies
- Benefits must exceed risks for the participant
- If it is necessary to use a placebo, the principle of "do no harm" must be respected
- Participants in the study must give their free and informed consent, as explained in Chapter IV (CNS 196/96) "Termo de Consentimento Livre e Esclarecido" (Freely Given and Informed Consent)
- There must be a system to assure privacy and confidentiality of information
- The study will preferably recruit autonomous individuals as study subjects. If vulnerable or disadvantaged persons are included, there must be specific mechanisms for their protection
- The study must respect social and cultural values
- If the participants have benefited from the treatment, they must have guaranteed access to the study products or therapy after the study is completed
- The study must benefit the participants and their communities
- There must not be any conflict of interest
- International studies must include Brazilian researchers and institutions, there must be an advantage to participants and the nation, and the study must have been initially approved in the country of origin
- Biological material and information obtained may only be used for the approved study
- Full attention must be guaranteed to participants; compensation may not be withheld in case of possible harm, and the only indications for dismissing a study subject would be for reasons of security or protection from greater risk
- Voluntary participants may not receive financial remuneration, but their study-related expenses (e.g. for transportation or meals) may be covered

CNS 196/96 was later expanded in response to experience gained from the most frequent ethical dilemmas, which generated discussion among those involved in bioethics and clinical research, and the reports of studies in different scientific areas (see Table 6.1). The National Health Council, through CONEP, passed Resolution 251/97 to address issues involving research for new medications, and Resolution 292/99, which relates to international projects. The latter (292/99) established that studies with international cooperation must include Brazilians as partners with shared responsibility for the implementation of the project; that no international project could take place without prior approval, and without the recruitment of participants in the country of origin; and if these conditions are not relevant to a study, the researchers must inform the Ethics Committee (CEP), which will evaluate if the benefits and risks are equitably distributed among the parties involved.

These standards, developed in accordance with requests from the government, the scientific community, study participants, and society in general, reflect the wishes of the citizens and the promise to defend human rights. Their objective is to assure that studies comply with ethical principles, and that the interests and well-being of individual human subjects take precedence over those of society and of science.

6.4 Health Regulations for the National Health Surveillance Agency

The National Health Surveillance Agency (ANVISA) is responsible for monitoring studies of bioavailability and bioequivalence, which are mandatory for the registration of generic medicines and other new medications. Resolution RDC N°. 103/2003 requires these studies to take place in certified centers, and there is an inspection program to guarantee quality (see Table 6.1).

More recently, Regulation RDC 34/2008 was approved. This regulation created a register of study participants and an information system covering studies on pharmaceutical equivalence and bio-equivalence to prevent volunteers from simultaneously participating in several trials, being exposed to unnecessary risks, or potentially biasing the study results (for example, by too frequent participation or by enrolling in more than one bioequivalency study at the same time). These issues had been addressed in Resolution CNS 196/96, which required participants to wait 12 months before enrolling in another study and prohibited payment for participation or for daily wages lost due to participation in the study. It was considered that these payments could unduly attract people from the lower socio-economic classes. The regulation did allow payment of expenses for meals and transportation, but there was no mechanism to ensure compliance with these standards and it had been noted that a large number of study participants came from vulnerable situations, seizing the opportunity to take part in clinical trials while ignoring excess risk. This is an important ethical problem, which has been inadequately discussed by the scientific community.

Table 6.1 Principal regulations in Brazil for the conduct of clinical trials

Year	Regulation	Authority	Major content	Current status
1996	Law N°. 9279	National Congress	Regulates the rights and obligations in relation to the protection of intellectual property	In force
1996	Resolution N°. 196	CNS	Ethical principles and standards for the protection of human subjects in clinical trials	In force
1997	Resolution N°. 240	CNS	Defines the inclusion of user representatives in the Committees for Research Ethics (CEPs)	In force
1997	Resolution N°. 251	CNS	Regulates research with human subjects for new pharmaceuticals, medications, vaccines, and diagnostic tests	In force
1999	Law N°. 9782	National Congress	Restructures the National System of Sanitary Surveillance, and created ANVISA	In force
1999	Law N°. 9787	National Congress	Generic medications	In force
1999	Resolution N°. 292	CNS	Regulates research directed by foreign companies, or which takes place with foreign participation	In force
2000	Resolution N°. 303	CNS	Regulates human reproduction research	In force
2000	Resolution N°. 304	CNS	Regulates research involving indigenous populations	In force
2003	Resolution N°. 103	ANVISA	Certification of centers that conduct studies on bioequivalence and bioavailability	In force
2004	Resolution N°. 340	CNS	Regulates research in the area of human genetics	In force
2004	Resolution RDC N°. 219	ANVISA	Regulates the authorization for clinical trials with medications and health products (later included in the standards for health surveillance)	Revoked
2005	Resolution N°. 346	CNS	Regulates multicenter projects	In force
2005	Resolution N°. 347	CNS	Regulates the storage of samples taken from human subjects, and the use of biological samples obtained during previous studies	In force
2005	Law N°. 11.105	National Congress	Creates the National Biosafety Council (Conselho Nacional de Biossegurança – CNBS), and restructures the National Technical Committee on Biosafety (Comissão Técnica Nacional de Biossegurança) (CTNBio)	In force
2007	Resolution N°. 370	CNS	Regulates the registration and accreditation, and the renewal of registration and accreditation, of the CEP's	In force

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Table 6.1 (continued)

Year	Regulation	Authority	Major content	Current status
2008	Resolution RDC Nº. 39	ANVISA	Regulates the approval and monitoring of clinical research involving medications and health products, revoking RDC 219/2004	In force
2008	Resolution Nº. 404	CNS	Standards for placebo use, and access to medications when a study is completed	In force
2008	Resolution RDC Nº. 34	ANVISA	Instituted the information system for studies of bioequivalence and bioavailability	In force
2008	Resolution Nº. 1885	National Medical Council	Regulates the use of placebos in research conducted by physicians	In force
2009	Resolution Nº. 421	CNS	Increases CONEP members from 13 to 15, ensuring representation by CNS Directors (including employees, managers, and users of the Unified Health System)	In force

ANVISA developed procedures for the approval of clinical trials with new medications (Phases I to III) and to grant permits for the importation of the experimental drug. As part of this process, ANVISA requests CONEP to provide information demonstrating that the proposed study meets the ethical guidelines established by the CNS and analyses the study protocol and the characteristics of the sponsor and institutions where the study will take place. If ANVISA is satisfied after reviewing these documents, it will release a special communication allowing the study to proceed and granting permission for the importation of the new medication for the implementation of the clinical trials.

Regulation RDC Nº 39, 2008, is currently governing the approval process by ANVISA (2008). It states that ANVISA must be informed of all adverse effects arising during the clinical trial, allows ANVISA to conduct inspections of the research centers – with or without CONEP- and apply sanctions if infringements of Best Clinical Practices are found. ANVISA also regulates the Contract Research Organizations (CRO's), which, through contracts with the study sponsors, facilitate the implementation of clinical trials in Brazil and are often responsible for all communications between the sponsor, ANVISA and the principal investigator.

The 2008 Regulation speeds the approval process for clinical trials by permitting simultaneous (or parallel) evaluation by CEP-CONEP and ANVISA instead of the previous sequential system (see Fig. 6.1). In this manner, ANVISA may approve the importation of experimental medications when the first Committee for Research Ethics (CEP) approves a multi-center project, without waiting for CONEP's approval, but the sponsor may not begin a study until CONEP's approval has been received. An enforcement mechanism must be established to ensure that this condition is met.

6.5 The CEP-CONEP System

The ethical evaluation of research involving humans is performed through the CEP-CONEP structure, which is part of the National Health Council (CNS). The final approval of clinical trials of new pharmaceuticals and other health products, as mentioned earlier, also involve ANVISA. Until recently, the CEPs of all the establishments where the study was to be conducted and the CONEP had to approve a project before ANVISA could authorize it and issue an importation license for the experimental drug or device to be tested in the trial. As mentioned in the previous section, a relatively recent change allows ANVISA to proceed with its work simultaneously with the CEPs' review, with the restriction that the sponsor may not begin the project until CONEP's consent has been received (see Fig. 6.1).

Both the CEPs and CONEP are agencies of *munus publicum* (i.e. their mission is for the public good); they are multidisciplinary and inter-professional, and include representatives of the users of the system; they function independently from the sponsor and the investigator, and they defend the interest and rights of the study participants. Committee members are volunteers who receive no employment contract or remuneration for their work on these committees, and are selected based on criteria of availability and commitment to ethical standards and defense of human rights.

The CEPs are collegial bodies created by the institution they serve and although they receive logistical support they are independent of the management of the institution. All CEPs must be approved by CONEP, based on pre-established criteria, and, with the principal investigator, are co-responsible in assuring that the research

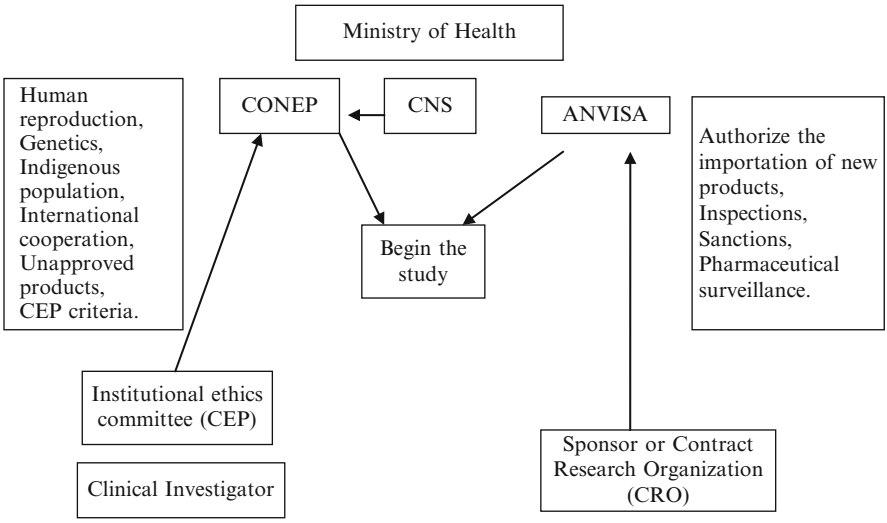

Fig. 6.1 The CEP – CONEP system and its relation to ANVISA

protocols comply with the ethical criteria established in the regulations. The CEPs are multidisciplinary, and must include specialists in health sciences, clinical sciences, statistics, and social and human sciences, with the restriction that members of the same professional category may not form more than half the committee. CEP members are elected for a three-year term; at least half of them are elected by their colleagues, and at least one must represent the users of the institution.

The CONEP is part of the National Health Council (CNS) and receives logistical support from the Ministry of Health, including travel expenses for members coming from different regions and institutions in the country, but administratively it does not report to the Ministry and is independent in decision-making. It consists of 15 members and 15 alternates chosen by the CNS from names provided by the CEPs, and each serves for a period of four years. Six members are selected by lottery, and nine based on their professional expertise. One member must represent health care workers, another the managers, and two members are the users of the National Health System (SUS). The CEP and CONEP coordinators are elected by the committee members.

The CEPs are responsible for the ethical review of all the projects taking place in their own institutions. CONEP examines projects approved by the CEPs that pose major ethical risks and meet the requirements to be classified as special projects, such as research in genetics, human reproduction, international collaboration, biosafety, those involving indigenous groups, and any project the CEP determines that should be evaluated by CONEP.

CONEP is also responsible for maintaining the register and supporting the CEPs, proposing additional regulations, and providing technical assistance. Since 2008, CONEP has the authority to make inspections of the implementation of clinical trials and of the CEPs together with ANVISA.

6.6 Initiating the System and Challenges to the Process

To assure functionally competent CEPs, establish common evaluation criteria, and standardize the decision-making process, CONEP listed the following actions:

1. Develop a national information system – SISNEP, a single data base of information about projects approved by the CEPs and by CONEP, accessible through the internet to researchers, CEP and CONEP members, and the general public. This system has been revised and renamed as Plataforma Brasil, and the general public can access to a subset of the information in the website http://aplicacao.saude.gov.br/plataformabrasil/login.jsf
2. Prepare a manual of procedures for the CEPs, with the participation of ten experienced CEP coordinators
3. Provide technical and financial support to strengthen and educate the CEPs, providing equipment and incentives for the local preparation of courses. This activity was also supported by the Secretary of Science and Technology in the Ministry of Health, which has also invested resources in the training of its members, and by the National Health Council (CNS), which sponsors annual

conferences of committee coordinators to discuss questions arising during the evaluation of protocols and other current concerns

CONEP monitors the performance of the CEPs using various strategies: (1) when they are first formed and they formally request to be recognized as a CEP, and when they renew their permit every three years; (2) by reviewing the annual reports submitted by the CEPs to CONEP, which include, among other important matters, the number and type of projects discussed, the number of meetings for project evaluation and the number of members present at the CEP meetings; and (3) by reviewing the CEP evaluations of special projects which need to be also submitted to CONEP. This double examination of special projects serves to assess the CEPs' compliance with the ethical regulations. In 2003, CONEP instituted a system for annual evaluation, recommending the suspension of committees that did not meet minimum performance levels (see Box 6.3).

Since this system was initiated, CONEP has revoked recognition to between two and 10 % of the CEPs annually. There is no doubt that this system is useful, but it is still not sufficient to ensure their appropriate performance and several proposals for improvement have been made. One of the suggestions is to promote exchange visits between members of different CEPs, but funding is absent. Currently, in compliance with Resolution RDC 39/2008, there are plans to make supervisory and inspection visits to the CEPs, in coordination with ANVISA, but there are problems with the allocation of funding and the training of personnel for this task. So it is still a work in progress, with the goal of establishing a supervisory system with regular and systematic oversight. Meanwhile, only sporadic inspections take place after specific problems requiring the attention of the national agency have been noted.

Box 6.3: CONEP Criteria for the Evaluation of CEPs

- Maintenance of the mandated composition of CEP personnel (Res. CNS 196/96, VII.4, VII.5) including representatives of the users of the system and informing CONEP of any changes that eventually become necessary
- Announcing the CEP decision on projects within the 30-day period proscribed by Res. CNS 196/96, VII.13.b
- Sending a six-monthly report to CONEP of all projects approved during that period
- Participation of more than 50 % of the CEP members in the meetings
- CEP meetings held at least once each month
- Having a designated place and time for the meetings to facilitate participation by researchers and study volunteers
- Maintaining a record of the sessions in an approved file
- Having an adequate, dedicated space to maintain confidentiality of all records and other documents
- Storage space within the institution to keep all CEP administrative documents and those of all reviewed projects for a minimum period of five years

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Box 6.3: (continued)

- Expectation of reviewing at least 12 projects per year; this estimate is based on projects evaluated in previous years
- When the CEP requests renewal of permission to operate, there must be proof that the CEP has an internal document governing its operation, approved during the first year following its registration
- There must be a designated administrative officer for the CEP, supported by the institution
- The CEP must have a fully equipped office with access to Internet, furniture, telephone, fax and office supplies
- Development of educational materials on research ethics, for CEP members, local researchers, and the community in general

At the end of 2007, 557 CEPs, involving 8,107 people, were operating in the principal research centers of the country. In 2005, CEPs evaluated 17,000 research protocols with a proposed recruitment of 600,000 study subjects. CONEP reviews annually between 1,000 and 1,500 special projects, which is less than 10 % of projects presented to the CEPs, signifying that the CEPs approve more than 90 % of research protocols involving human subjects. The majority of projects reviewed by CONEP involve new medications, and are often multicenter international studies, followed by studies in the area of human genetics, most of which include testing for genetic problems, the search for polymorphisms in certain populations, and the use of stem cells.

6.7 An Evaluation of the System After 12 Years of Experience

Twelve years after Resolution CNS 196/96 was approved, a large number of institutions have supported the CEP/CONEP system, which has facilitated the gathering of information about research involving humans that has taken place in the country, the establishment of a system to protect research participants – specially vulnerable populations, and the development of procedures for the ethical review of the research protocols and for prohibiting or suspending studies that do not conform with ethical guidelines. The system has been institutionalized rapidly, and without doubt has protected human subjects and prevented abuse.

In 1996, the first year of the system, CONEP classified 70 % of special projects that had previously received CEP approval as “opinion pending”. CONEP could not give its final approval to these studies because they did not conform to the regulatory requirements, had missing information, or did not comply with ethical

requirements. The other 30 % applications were approved. Between 1996 and 2002, the proportions were reversed, and by 2002, 70 % of proposals evaluated by CONEP were approved, less than 30 % were pending, and between 1 and 4 % were refused. The most common problems were incomplete protocols, inadequate informed consent forms, incomplete information about the preliminary phases of the study, and inadequate risk-benefit analysis (Freitas et al. 2005). This progression was predictable, and corresponded with the period of training for the CEPs. After 2003, however, the proportion of studies classified as pending, or refused by CONEP, increased. In 2008, CONEP initially approved 45 % of projects, refused 15 %, and classified 34 % as pending, while the remainder did not meet the requirements for review by CONEP (Ministério da Saúde 2009). This apparent regression in the performance of the CEPs reflected CONEP's growing emphasis in minimizing the use of placebos, obtaining guarantees for the continuation of treatment after the completion of study, and requiring insurance policies to compensate participants for the possible adverse effects linked to their participation in the study. Several sources also stated that the CEPs had more difficulty meeting the guidelines and overcoming pressures from researchers and sponsors. These circumstances generated some friction between several CEPs and CONEP, contributed to delays in the process of approving projects (especially those involving new medications), and explained the pressure from the pharmaceutical industry to eliminate CONEP's participation in the review of international projects.

Compared with other countries, according to Hirtle et al. (2000) the Brazilian system of ethical review has several strengths, including the location of the CEPs in the research centers, the legitimacy of the system, the performance of the CEPs, and the attention given to avoiding conflicts of interest.

6.7.1 The Location of the CEPs

In Brazil, the CEPs are located in the institutions where research takes place, and are coordinated at the central level. The large network of institutionally-based CEPs in Brazil inhibits the organization of commercial ethics committees (also known as independent committees), and helps researchers identify the CEP that will oversee the study. The increased presence of commercial ethics committees in other countries in the region is a concern for Brazilians, who think that commercial interest, and the need to satisfy their sponsors, may affect the speed with which they carry out their duties and compromise the safety of the study participants (Lemmens and Freedman 2000). Other advantages of the institutional committees include the following: CEP members have easy access to researchers and study subjects, which facilitates reviewing and monitoring the implementation of research protocols; CEPs can educate the scientific community and the users of the services; they stimulate institutional research and discourage the implementation of isolated studies with little potential to have significant impact in the health of the community.

The legitimacy of the system is of crucial importance because it builds trust in the ethical review. There are two conditions for a system to have legitimacy: (1) the process of forming the ethics committees, and (2) the clear establishment of a locus of responsibility and a decision-making mechanism to govern committee operations. As we have seen, committee members must be democratically elected and include representatives of users of the health system as well as experts in the different disciplines to ensure that the evaluation of study protocols is done with the necessary scientific and ethical rigor. The functions of the CEPs and CONEP are well defined in the resolutions of the National Health Council (CNS), especially in Resolution 196/96, which includes – in addition to guidelines for the ethical analysis of the protocol – the standards that govern a good part of the operational process, which are described in detail in the Manual of Procedures of the CEP.

In practice, the system has some deficiencies. For example, in-depth surveys of 188 people nominated by the CEPs to be part of CONEP revealed the following: more than 40 % of those interviewed said that the representatives of the users of the system participated and contributed little to the discussion of the protocols, and were not invited to provide written reports about the projects; and 10 % reported that meetings took place without a quorum of 50 % of members present (Freitas 2007). This is a problem in other countries also, and shows that support must continue, both to stimulate participation by the general public and to increase the ability of the system to democratize the decision-making processes of the CEPs.

From the perspective of system users, one factor, which threatens the legitimacy of the system is the issue of confidentiality of discussions within the CEPs and the CONEP. These are not public meetings; only the name of the institution where the approved project will be implemented is released, and information about rejected or suspended projects is known only to the CEPs and researchers who are directly involved. This protects the interests of the sponsors, who can move the project to other institutions or countries with less strict regulations. This matter must be discussed thoroughly, as it affects everyone.

6.7.2 Conflicts of Interest

The institutional ethics committee must be independent in its decision-making, and not only assure the protection of the rights and welfare of study participants but also generate public confidence in the system. Many factors influence the independence of institutional ethics committee members, including the role and responsibilities of whoever appoints the committee members. There is concern about the independence of CEPs that serve clinical research groups or institutional groups, which financially benefit from research projects, because pressure may be placed on the CEPs to approve projects that could contribute to the financial or other goals of the institution. For this reason, it is very important to ensure that the ethical review system is totally independent of institutional pressure, which is not an easy task.

Freitas (2007) documented that 48 % of CEP members who had been nominated as candidates for CONEP were holding administrative and management positions in their institutions, and 18 % were directors of the research area, therefore also responsible for increasing institutional research. Most were professionals with research experience, and 26 % had participated in clinical trials sponsored by the transnational pharmaceutical industry.

The Brazilian system does have checks and balances, which help reduce the influence of conflicts of interest and the possibility that sponsors manipulate the institutional CEPs. For example, (1) the CEP-CONEP structure reports and is overseen by the National Health Council (CNS). The CNS is an organization with community participation and social control, and acts as a bridge between the government and the people in general – 50 % of its members represent system users, and 50 % are health care workers; and (2) the CEPs coordinate with a central office – CONEP – which in turn is accountable to the CNS. Other countries with older control systems, e.g. Canada and Germany, say that the lack of a central office has been a weakness of their system and Germany has recently established such an office.

In summary, the Brazilian system has seen continuous development and has tested the ability of the national level to support the process. Much progress has been made although challenges remain. As mentioned, CEP members must not have an administrative appointment in the institution supporting a CEP, must have at least a minimal level of training in research ethics, and must be elected by their peers. The committee coordinator must be democratically elected by the committee members, and the participation of system users must be increased, be it in numbers or in ways to facilitate their active participation in CEP discussions and decision-making.

The system could continue to gain strength if the exchange of opinions and experiences among the CEPs, and between the CEPs and CONEP, was fostered. Greater interaction among CEPs with different levels of experience and development could lessen the pressure on CONEP to guarantee the integrity of the system. These activities should be part of the continuing training and support programs.

6.8 Conclusion

Ideally, clinical trials will increasingly abide by internationally accepted ethical requirements, be focused on the health of Brazilians, and benefit all participants – patients, health professionals, hospitals, universities, and regulatory agencies. Planning and investment in the system is necessary to continue to advance clinical research regulation in Brazil. As Brazil becomes more attractive for clinical research and increases the number of researchers who meet international standards, concern for the respect of ethical standards increases. Current regulations and the creation of the CEP/CONEP system demonstrate that the nation is well able not only to develop guidelines, but also to apply ethical principles through clinical researchers and the hundreds of CEPs that are distributed throughout the country. There is still much to be done, and it is important to reflect on the shared

responsibility of ensuring the sustainability of the system of ethical review of research projects.

It should be noted that the CEP is a legitimate area for democratic debate, and has an important social role from which to draw lessons that according to Gutmann and Thompson (1997) may be applicable to other public policy areas. For example, for endorsing the legitimacy of collective decisions, supporting the value of activities carried out in the public arena, making decisions based on mutual respect when there are different and diverse interests, and also incorporating strategies to permit the correction of errors, on the part of citizens and professionals, which occur when there is an incomplete understanding of the problems that may arise during the planning and implementation of research studies.

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