

# Ethical Conduct in Research Involving Human Beings In Brazil

## *Diagnosis of Research Ethics Committee*

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**Objective:** Diagnose ethical conduct in research involving human beings in Brazil and the last 10 years of activity by the Human Research Ethics Committee of the Health Department - Federal District - CEP/SES/DF.

**Methods:** This work was based on a documentary research, descriptive and retrospective. It examined the database containing records of cases brought before the CEP/SES/DF, corresponding the period of June 1997 to December 2007. Results were generated in Excel program, version 2007.

**Results:** CEP/SES/DF has presented increasing number of research projects submitted to appreciation (n = 1129), composing: 90.4% approved 1.7% disapproved, 7.4% removed/filed and 0.5% excluded. Of these projects, 83% belonged to Group III, 18% multi-centered projects and 10% protocols with foreign participation. Time for approval has decreased over the years (30 to 60 days). Frequent pendencies: End of Free and Informed Consent (30%), Cover Sheet (25%), Methodology (20%), *Curriculum vitae* (12%), Budget (9%), and Others (4%).

**Conclusion:** The assessment of the CEP/SES/DF activities, during a ten-year period has shown its commitment to the legitimacy of research ethics review and scientific production SES/DF. There were some weaknesses such as difficulty in monitoring the accompaniment of the research; interruption of works due to adverse drug reaction; gaps or errors in the protocol submitted by the researcher. These situations are the achieving targets for the elaboration of specific criteria.

**Key-words:** clinical research; ethics conduct in research in Brazil; evaluation.

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## INTRODUCTION

Brazilian regulations concerning research involving human beings, has followed international trends encouraged by the production and dissemination of international ethical guidelines on the subject. Among those documents are, the Code of Nuremberg (1), the Declaration of Helsinki (1964, 1975, 1983, 1989, 1996, 2000) (2), the Belmont Report (1978) (3), and the International Ethical Guidelines for Biomedical Research in Human Beings (1982) (4). These statements discussed themes such as respect for people, the need for informed consent of participants in the research; provided understanding of the balance between benefits and risks involved in the realization of the study, recommendations for research recruiting special populations such as children, pregnant mothers, mental illnesses bearers, prisoners and equitable selection of subjects.

The first Brazilian research regulation involving human beings was Resolution No. 01/1988 of the National Health Council (CNS), a body linked to the Ministry of Health (MS) (5). This document laid down the necessary ethical requirements for research development in the field of health in the country.

In 1996, the Southern Common Market Treaty (Mercosur) prepared Resolution No. 129/96, entitled Good Clinical Practice. This resolution focused on clinical

pharmacology research regarding authorization, monitoring, responsibilities of researchers and sponsors, ethical requirements and the need for the obtainment of pre-clinical and clinical information of the drugs being studied, as a way to ensure the protection of participants included in the following steps of experiments (6).

Research Ethics Committees – Comitê de Ética em Pesquisa (CEP) started to appear in Brazil in hospitals, clinics and specialized services. These committees were distinguished from discussion, institutes and other places where ethics was the subject of debate and education. They had the task of gathering men and women of science, lawyers, philosophers, even ordinary citizens who were able to contribute with different views in determining the ethical reasons related to the challenges posed by research carried out with human beings.

However, its legal format and composition were not well defined (7). Resolution 01/88 did not obtain the regulatory outcome expected by the scientific community in this field. As a result, the need to draw up a new national document addressing the ethical requirements essential for the execution of research has arisen (8). After a year of intense debates, in 1966, CNS/MS published Resolution 196/96, entitled Standard Guidelines and Regulatory Research Involving Human Beings, now in vigor (9,10).

With rapid scientific and technological development, ethical reflection on research protocols could not be restricted to the requirements of Resolution 196/96. There

was a need to elaborate additional guidelines in order to deal with issues related to thematic areas such as resolution CNS 251/97 (area of new drugs, vaccines and diagnostic tests); resolution CNS 292/99 (memoranda of cooperation with foreign research); Resolution CNS 301/00 (ensure the best proven diagnostic or therapeutic treatment); resolution CNS 303/00 (area of human reproduction); resolution CNS 304/00 (area of research with indigenous peoples); resolution CNS 340/04 (research in human genetics); resolution CNS 346/05 (multi projects of special subject area, group I); resolution CNS 347/05 (storage or use of biological materials); resolution CNS 370/07 (registration and accreditation of CEP in Conep and registration renewal) (11).

The CEP/SES/DF is a multidisciplinary and cross collegiate body, a consultative, deliberative, legislative, educational, independent and for the first time registered at the National Research Ethics Commission (Conep) of the Health Ministry (MS), 18 June 1997. Subsequently, its accreditation has been renewed, and it has been operating since then. The Rules of Procedure of CEP/SES/DF is set in the Ordinance No 138-SES/DF of 15/12/2005 (12-15).

CEP evaluates research projects that are carried out under SES-DF, which currently have an administrative structure of 18 hospitals, 69 centers for basic health care, one Foundation for Education and Research, which includes the Technical School of Brasilia (training of technicians and assistants in different areas of health) and the Medical School and the Nurse School of Health Science (ESCS/FEPECS); graduate courses in different areas; Central Laboratory of Public Health, Hemocenter Foundation.

The CEP/SES/DF is composed of 26 representatives of services related to the Department of Health, with 6 doctors, 3 pharmacists, 2 biologists, 2 psychologists, 1 dentist, 1 social worker, 1 administrator, 1 lawyer, 1 pedagogue, 2 nutritionists, 2 nurses, 2 representatives

of users and 2 representatives of the voluntary services of SES.

The objective of this work is to diagnose the ethical conduct in research involving human beings in Brazil and the 10 years of activity of the CEP/SES/DF assessing the following aspects: nature of the projects examined; professional category of the main researcher; areas of concentration of the research; time for approval of protocols; number of projects approved, disapproved and withdrawn; most frequent pendencies in protocols, among other parameters.

## METHODS

The work is constituted of a documentary research, descriptive and retrospective, in case study modality. The project was approved by the CEP/SES/DF under protocol number 52/08. During data collection and disclosure of results, confidentiality and secrecy were assured to both projects and researchers.

The descriptive assessment indicated the dimension of all projects entered the protocol at CEP/SES/DF from June 18, 1997 until December 31, 2007. We analyzed CEP database information, coupled with data contained on the cover sheets of protocols submitted. The data was allocated in system and the results generated in Excel program, version 2007.

## RESULTS

The Ethics Research Committee of the State Health Secretariat - Federal District (CEP/SES/DF) has increased steadily in number of research projects submitted over the last 10 years (Figure 1).

During CEP existence, 1129 projects were submitted

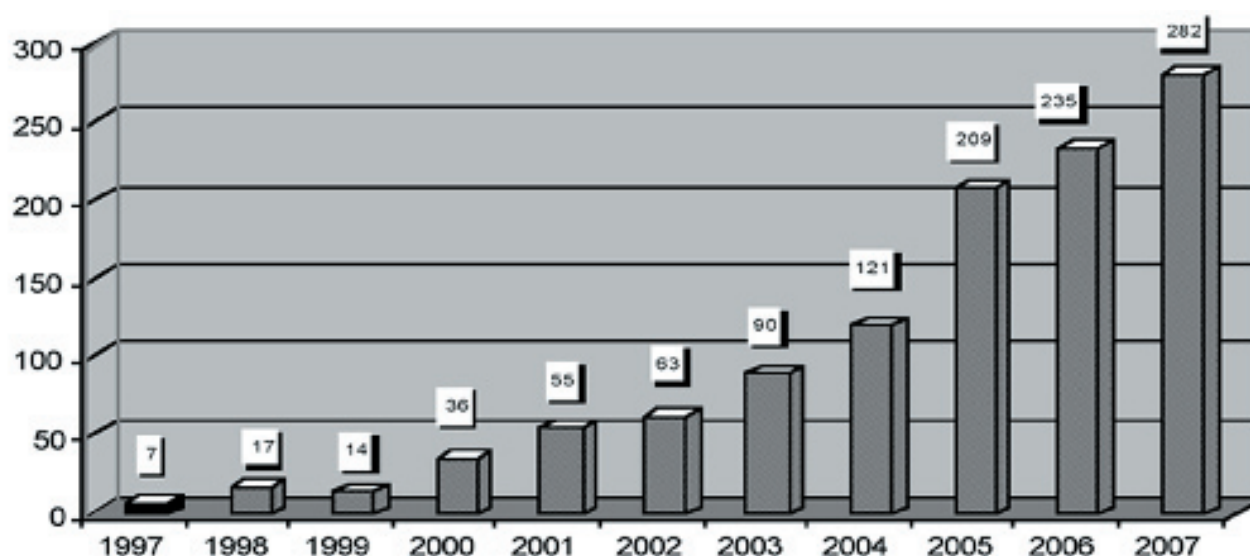


Fig. 1 - Projects submitted to the CEP/SES/DF in the period from 18/06/1997 to 31/12/2007 (N=1129).

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Location/Period	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	Total	%
<b>Submitted</b>	7	17	14	36	55	63	90	121	209	235	282	1129	100
<b>Approved</b>	4	15	10	25	45	53	83	115	195	206	270	1021	90.4
<b>Not approved</b>	0	0	0	6	2	2	2	1	3	1	0	17	1.7
<b>Withdrawn/closed</b>	0	0	4	5	8	6	5	5	11	28	12	84	7.4
<b>Excluded</b>	3	2	0	0	0	0	0	0	0	0	0	5	0.5

to its appreciation, and from those, 1021 were approved, that is, 90.4% of approvals out of all protocols submitted (Table 1). Only 1.7% of projects were rejected on account of the fact that researchers failed to comply with ethical requirements needed to carry out researches with humans.

Due to the specific characteristics of some special thematic areas, there was need for the formulation of complementary guidelines to Resolution 196/96 CNS for these themes (8). The classification specified by Conep involves groups I, II and III.

In Group I projects are included in the Special Thematic Areas such as: human genetics, human reproduction, new equipment, supplies and devices, new procedures; indigenous peoples; bio-safety; research with foreign cooperation and research projects recommended by the CEP collegiate. Group II includes thematic areas projects

such as new drugs, vaccines and diagnostic tests. Group III includes all protocols of research which do not fall into any special areas listed in other groups.

Of the projects submitted to CEP, the majority of them (83%) were inserted in Group III. Whereas other protocols were thus distributed: 12% in Group I and 5% in Group II. The percentage allocated to Group II is possibly due to lack of sponsors, inadequate facilities for the development of the project, long duration of the research and the need for skilled human resources.

Group III presented greater frequency of protocols submitted to the CEP/SES/DF suggesting that researchers adapted to the conditions of the research offered by the Department of Health of the Federal District. This group does not require additional approval by Conep.

Resolution 346/05 CNS deals with aspects related to the appreciation of multi-centered research projects.

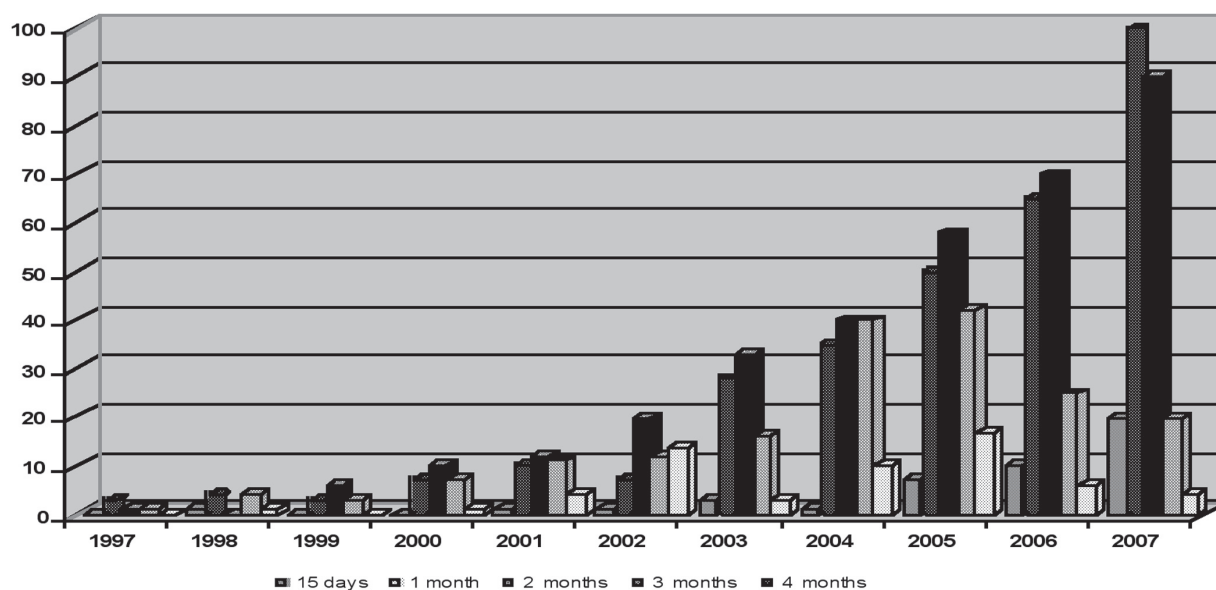


Fig. 2 - Time for approval of projects submitted to the CEP/SES/DF in the period from 18/06/1997 to 31/12/2007 (N=1129).

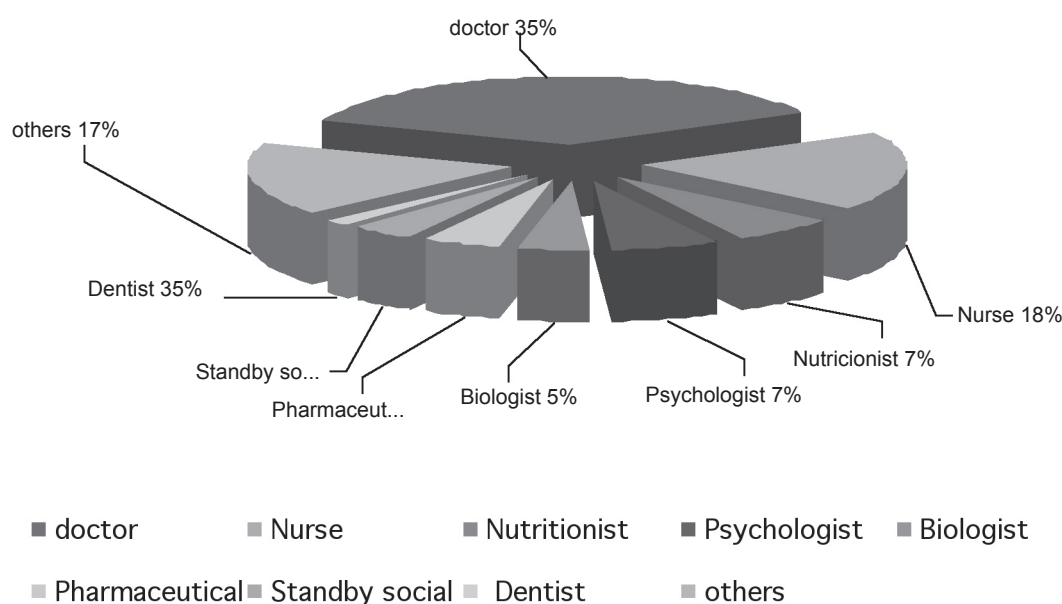


Fig. 3 - Professional cathegory of the researcher responsible for the project submitted to the CEP/SES/DF in the period from 18/06/1997 to 31/12/2007 (N = 1129).

Other (17%) = architect, anthropologist, biomedical, physical educator, administrator, lawyer, librarian, fire, civil engineer, epidemiologist, journalist, pathologist, teacher, chemical, sociologist and microbiologist.

Multi-centered studies include all studies conducted at different centers, located at different geographical points, carried out simultaneously though utilizing the same research protocol. Under this category, the CEP / SES / DF received for its appreciation 18.0% of multi-centered projects during the assigned period search.

Resolution CNS/MS 292/99 treats researches coordinated abroad or with foreign cooperation. Traditionally, these searches are linked to multinational companies belonging to pharmaceutical and medical areas. The majority of them are directed towards comparative studies by means of randomized clinical trials, evaluating new drugs and technologies, procedures or medical and hospital equipment.

However, among protocols submitted to the committee, researches supported by foreign grants accounted for 10% of protocols assessed during the study period, whereas the majority of these investigations were inserted into international multi-centered studies.

As far as sponsorship concerns, researchers reported that all other research projects received financial support from public governmental institutions, or resources provided by the researcher himself or from the institutions he was entailed to.

The Committee is in charge of the evaluation of the protocol for the first 30 days, and returns the protocol back to the researcher according to the following modalities: project approved, pending or refused (8). For pending projects the researcher has up to 60 days to consider

them. This period finished, the researcher receives correspondence informing the status of the protocol, warning him that it may be filed for lack of response. The deadline for the evaluation committee to emit CEP's final opinion, ranged between 30 and 60 days. Over the last three years, the period of analysis has decreased (Figure 2).

The most frequent pendencies presented in projects evaluated by the CEP collegiate refer to the following items: request to reassessment of TCLE (30%), Cover Sheets (25%), Methodology (20%), Schedule Budget (12%), *Curriculum Vitae* (9%), Other Factors (4%). The TCLE has also been reported by other CEPs as the major cause for pendency in approval of protocols (16-19).

The projects appreciated by CEP in the referred period, mentioned the multidisciplinary participation of researchers who were listed according to different categories of the health area whose protocols they were responsible.

## DISCUSSION

The increasing demand for protocols validated by CEP/SES/DF is based on the assumption that its advisory and educational designations, determined by Resolution CNS 196/96, will ensure researchers with continuous education (8).

A very important information conveyed among researchers, indicates that research projects should be submitted to CEP before it begins. This reason owing to the fact that both indexed scientific journals as well as na-



tional and international development fomenting agencies requires a letter of approval by CEP for the publication of articles or liberation of financial resources.

Another relevant factor that has possibly contributed to the increasing number of projects submitted to CEP/SES/DF, was the demand for graduate and postgraduate courses, mainly in the area of health science which stimulate studies in humans. This shows an important link between CEP and researchers, CEP operating as consultant for ethical conduct in research complying with recommendations by the CNS Resolution 196/96, whose objective is to ensure the integrity of subjects enrolled in the research.

A project can be defined as "not approved" when there is a matter ethically wrong, not acceptable, that would demand a radical modification of the protocol. The percentage of projects "not approved" was only 1.7% as shown in Table 1. The low percentage of non-approved protocols is a reflection of educational actions undertaken by the CEP.

The ethical analysis by CEP should be emitted in 30 day's time (8). The CEP/SES/DF has met the recommendations of Resolution 196/96, issuing opinion and final evaluation of protocols in a period of 30 to 60 days, if the researcher is fast to respond to pendencies.

A weak point observed in the works performed by CEP in Brazil refers to the monitoring of protocols approved. The committee members should have more availability to supervise the course of proceedings in researches. This is a critical situation, since there is no work bond between members and CEP, the link being only honorific and tasks related to protocol evaluation are just a sideline activity for the members. Nevertheless this is an essential attribute of the system, created to ensure that participants of the research will receive the approved version from TCLE and the implementation of the research will be carried out in accordance to the ethical requirements adopted by CEP.

Another limitation about CEP's works is the follow up of a decision to discontinue the search at the occurrence of adverse reactions (ADRs) with casualty attributed to the drug under study. These events may have occurred at the coordinator study center in Brazil or abroad, in case of multi-centered studies and notified by the researcher to CEP. The committee does not conduct investigations in order to verify what caused the casualty and severity of ADRs informed by the researcher.

In reference to adverse events, CEP operations are limited in Brazil at present. Its function is limited to taking note of the occurrence, requesting information from the researcher regarding the procedures performed as to minimize the effects of complications and reactions, considering the principle of nonmaleficence, besides forwarding notification to competent bodies such as National Agency of Sanitary Vigilance (ANVISA) and Conep for the due measures under its jurisdiction.

In the protocols of clinical pharmacology for the development of new drugs (stages I to III), after notification of the occurrence of a RAM, the document should

be forwarded to the Research Management Clinic and at phase IV (post-marketing) the Pharmacovigilance Management office should be informed. Both departments belong to ANVISA and are supposed to take the appropriate measures.

The CEP/SES/DF has received reports of researchers responsible for clinical studies of deviations and errors in the protocols approved. Many refer to matters related to the following aspects: difference in the timing of medication taken by participants, lack of laboratory tests or procedures in specific periods that should have been done but have not been. Such deviations may have occurred in differentiated centers in Brazil or abroad, when the study was multi-centered. In such cases, the CEP/SES/DF have questioned the researcher on the conduct adopted to prevent or minimize the occurrence of such abuses and to minimize risk and harm on the participants.

The activities undertaken by the CEP/SES/DF in the period of 10 years showed that the committee excelled its performance in dealing with research ethics review of protocols. This proves its legitimacy as a forum to ensure the protection of research participants, although the committee cannot guarantee the ethnicity required for its implementation, since the monitoring process is achieved by partial and final reports submitted by researchers.

The diagnostic evaluation of this research was made possible through data filed at CEP/SES/DF since its creation. Information on the protocols examined by a CEP should never be discarded without a detailed diagnostic evaluation of activities in order to qualify the process and the actions taken.

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