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SUMMARY

presentation

In recent years, the profile of research related to the biomedical field in Brazil has significantly changed. Investigations with stem cells, genetic engineering, new reproductive technologies and other topics related to the accelerated scientific and technological development have become part of the daily life of public and private institutions that work with the subject. Initially restricted to scientific circles, such investigations are now scheduled by the media and debated throughout society, which was unthinkable a few years ago. The discussions reach the Government, the Legislature, the Judiciary and the population itself, which, in the final analysis, is the one who receives the impacts (and benefits...) of this vertiginous process.

An example of this was the recent controversy related to the Biosafety Law, which authorized research with embryonic stem cells in the country. Different sectors of society came out in public to manifest themselves in favor or against the proposal, with various technical-scientific, ethical, religious arguments, etc.

The National Health Council (CNS) assumed, almost two decades ago, the responsibility of debating the ethical aspects related to research involving human beings. By monitoring this delicate evolution and regulating the projects under development, the CNS aims, in addition to preventing abuses and protecting research subjects, to contribute to the safe development of investigations that can really benefit Brazilian society.

out.

Since 1996, the country has had Resolution No. 196/96 of the CNS, which regulates the functioning of the sector. According to this Resolution, all research in progress in the country that involves human beings must necessarily be submitted to the appreciation of specially accredited Research Ethics Committees (CEPs), under the superior coordination of the National Research Ethics Committee (Conep) . This, in addition to controlling the national system for evaluating investigations, analyzes special cases and has the critical responsibility of being constantly updated with regard to protocols and international agendas in this field.

In this way, the CNS, with the support of an entire complex support structure composed of Conep and the local Committees, fulfills its priority goal of ensuring that all research with human beings in Brazil is developed in an ethical and safe way, protecting the integrity and the citizens' rights of volunteers.

Eliane Aparecida da Cruz
Executive Secretary
National Health Council

Introduction

It is characteristic of the human being to ask questions to Nature – it can It can be said that this behavior is what sets it apart from other animals.

When formulating questions, the human being “anguishes” looking for answers that can come in the form of a scientific truth, a theory, a hypothesis, a neologism or a myth.

Thus, the human being, at the same time that he behaves like a “philosopher” (asks questions), he also has a “researcher” (seeks answers). It is the inevitable destiny of the human being, therefore, to be an “eternal researcher”; it is your destiny to seek new knowledge.

In this search, the human being had to become aware of the other and the world and, consequently, had to reflect on the question of “human values”. And so, in addition to worrying about “philosophy” and “research”, he also had to deal with ethics.

Despite the existence of ancient codes, such as that of Hammurabi, and of moral behavior, it was only practically 50 years ago that human beings sought to prepare a specific document on ethics in research involving human beings, the Nuremberg Code.

The implementation of the document was a consequence of the imperative need to substantiate the judgment of the Nuremberg Tribunal. It is ironic that, because the Code was drawn up *after* the crimes, the abusive experiments were actually condemned on the basis of general administrative provisions of Nazi Germany itself.

In any case, the Nuremberg Code was of great importance, effecting, above all, respect for the self-determination of human beings (autonomy).
The Nuremberg code, from 1947 onwards, became a basic document, as a guide for medical research, for almost all countries and medical research centers.

Unfortunately, the abuses did not cease to occur; in the 60's, several articles with serious ethical distortions were published in medical journals of the highest level. At that time, the World Medical Association, meeting in Helsinki, in 1964, elaborated additional norms to the Nuremberg Code and that even journals in the meetings of the World Medical Association continue with the name of Declaration of Helsinki, already established throughout the world.

In the early 1980s, as ethical problems persisted in biomedical and behavioral research, the World Health Organization, together with the Scientific Councils of medical organizations, published the “International Guidelines”. This is yet another document, of international value, prepared by doctors and directed, now, to the biomedical area and not just the medical area.

From the Nuremberg Code, several countries, also signatories of the other documents, established norms, laws or complementary codes, using different systems.

In Brazil, in 1988, at the right time, the National Health Council (CNS) edited Resolution No. 1/88, basically referring to the subject of medical research. In 1986, in fact, the subject was being, albeit discreetly, discussed in medical research settings; in 1987, a book was published on the subject, calling attention to the need for a deeper discussion on the ethics of research in human beings.

Resolution No. 1/88 undoubtedly constituted an important step within the theme. The Resolution merged ethical issues with issues of Health Surveillance and biosecurity. Unfortunately, there was little adherence to the regulations contained therein. Thus, in 1992, a survey carried out by the Federal Council of Medicine (CFM) showed that the number of medical research centers that complied with the provisions of the Resolution was small.

It is worth remembering, by the way, that Resolution No. 1/88 assumed that there was direct parallelism between the level of research and ethical adequacy, by stipulating the “privileges” for research carried out in Graduate Centers with “Concept A by Capes” . In reality, world experience, unfortunately, does not support this point of view.

Against this background, members of the National Health Council, in 1995, highlighted the need to review Resolution No. 1/88 and establish norms for research involving human beings. Once the proposal was approved, an Executive Working Group (GET) was appointed for this purpose.

By reviewing the literature on the subject, analyzing documents from different countries, taking into account the contribution in the various segments of society requested by the GET, it was possible to arrive at the elaboration of CNS Resolution No. 196/96.

CNS Resolution No. 196/96, as it is recognized, is one of the few documents of an essentially bioethical nature, in the broadest sense of pluralism. This characteristic existed in the genesis of the Resolution, embodied in its doctrinal content and in its operationalization.

The international documents were prepared by doctors and are concerned with research in the medical area or at best biomedical.

The Resolution was prepared based on multi and interdisciplinarity, covering suggestions from different segments of society (including research subjects) and is concerned with research involving human beings in any area of knowledge and not just with medical research.

A fundamental characteristic of CNS Resolution No. 196/96 lies in the fact that it is neither a moral code nor a law. It is a piece of a bioethical nature, which means analysis and critical judgment about values (which may be in conflict), which requires basic conditions for that. Thus, freedom to make choices, non-prejudice, non-coercion, greatness to change one's option, humility to respect the other's option, are essential conditions for the exercise of bioethics.

The activity of the Research Ethics Committee (CEP), which is multi and interdisciplinary, identifying conflicts of values, critically reflecting on dilemmas, analyzing the ethics of research, having as its basic foundation the protection of human dignity, is a task of the most relevant and, not infrequently, “distressing”. It is, however, the “anguish” motivated by the ability of each one to review himself, analyze values and establish options.

As proof of respect for the work of the CEPs, the National Research Ethics Commission (Conep), with the support of the CEPs themselves, in solidarity with the enormous burden of ethical responsibility of each of its members, triggered the elaboration of this Manual, as way of encouraging the achievement of each Committee's mission. It is a set of guidelines as subsidies for the functional organization and, consequently, for the better performance of the Research Ethics Committees.

This is a preliminary text that should continue to be improved by the CEP members themselves, in light of their experiences within the Committees. Conep expects to receive contributions in this regard.

We thank all those who made this manual possible: members of Conep, CEPs, Executive Secretariats of Conep and CNS, DECIT/SPS/MS and invited advisors.

William Saad Hossne
Coordinator
National Research Ethics Commission

1 Research Ethics Committee (CEP)

1.1 Definition

The Research Ethics Committee (CEP) is an interdisciplinary and independent collegiate, with a “public munus”, which must exist in institutions that carry out research involving human beings in Brazil, created to defend the interests of research subjects in their integrity. and dignity and to contribute to the development of research within ethical standards (Regulatory Norms and Guidelines for Research Involving Human Beings - CNS Res. No. 196/96, II.4).

1.2 Role

The CEP is responsible for evaluating and monitoring the ethical aspects of all research involving human beings. This role is well established in the various international ethical guidelines (Declaration of Helsinki, International Guidelines for Biomedical Research Involving Human Beings - CIOMS) and Brazilian (Res. CNS n.º 196/96 and complementary), guidelines that emphasize the need for ethical and scientific review of research involving human beings, aiming to safeguard the dignity, rights, safety and well-being of the research subject.

In this way and in accordance with Res. CNS n.º 196/96, “all research involving human beings must be submitted to a Research Ethics Committee” and it is up to the institution where research is carried out to establish the CEP.

The CEP's mission is to safeguard the rights and dignity of research subjects. In addition, the CEP contributes to the quality of research and to the discussion of the role of research in institutional development and in the social development of the community. It also contributes to the appreciation of the researcher who receives the recognition that his proposal is ethically adequate.

The CEP, by issuing an independent and consistent opinion, also contributes to the educational process of researchers, the institution and the committee members themselves.

Finally, the CEP plays an advisory role and, in particular, an educational role to ensure the continued education of the institution's researchers and to promote the discussion of the ethical aspects of research on human beings in the community. Thus, it should promote activities such as seminars, lectures, journeys, courses and study of research protocols.

1.3 Scope

The CEP is an institutional body and is primarily responsible for appraising the research protocols to be developed in its institution. Its scope must be defined in the Internal Regulations, especially when there is more than one CEP in the same institution. However, two other situations can be raised: the assessment by the CEP, at the request of Conep/CNS, of protocols to be carried out in other institutions that do not have a CEP or the assessment of research protocols that, being developed within the scope of postgraduate studies, need to be evaluated by the CEP of the researcher's home institution and by the CEP of the institution where the research will be carried out (responsible for recruiting subjects or collecting data). Additionally, it should be noted that when carrying out multi-center or collaborative studies, the research protocol must be assessed by the CEP of each center where the study will be carried out, reflecting the institution's responsibility for the research subjects and the responsibility of the institutional CEP. The assessment must be independent, and the results of the local CEP must be respected, which may conclude whether or not the protocol is approved, coinciding or not with the assessment of another CEP.

As for the appraisal of projects to be carried out in other institutions, it should only be done after an indication obtained by the researcher directly from Conep.
In addition to evaluating the ethics of research projects, the CEP becomes co-responsible for their development, also highlighting the educational and consultative role with researchers, institutional community, research subjects and the community in general. To perform these functions well, the CEP must be institutional and the Res. CNS n.º 196/96, item VII.2, provides that “If it is impossible to constitute a CEP, the responsible institution or researcher must submit the project to the CEP of another institution, preferably among those indicated by the National Ethics Commission in Search". This indication takes into account the subjects' access to the indicated CEP, the possibility of monitoring the project, the institution's profile, the CEP's ability to receive additional demand, the CEP's compliance with the norms and the researchers' enrollment in the respective professional councils, seeking to indicate a CEP in the same municipality. Thus, Conep does not give up this indication.

The CEP must have an administrative employee responsible for assisting researchers and other interlocutors, including for receiving research protocols, with a fixed location and time published within the institution. An agenda of meetings for the year must also be disclosed with deadlines for submitting projects, considering that the CEP must issue an opinion within 30 days (Res.
CNS n.º 196/96 - VII.13 / b).

2 Implementation of the CEP

Every institution where research involving human beings is carried out must constitute a CEP. This system began in health institutions, but with Res. CNS n.º 196/96, which covers research involving human beings in any area of knowledge, several institutions from other areas, such as law, sociology, education, anthropology, etc. have created their Research Ethics Committees.

It is up to the institution's management to take the initiative to create and organize its CEP. The Res. CNS No. 196/96 defines the general characteristics of the Committee, its composition and attributions. It also establishes that the CEP must be registered with the National Research Ethics Commission (Conep), which will analyze the documentation sent along with the registration request, which must contain: form with the list of members and institution and coordinator data; act of creation of the Committee by the institution's board of directors; brief description of the requesting institution's mission and general activities, including those related to research; and document from an organized civil society entity presenting the user representative (CNS No. 240/97). Conep evaluates and sends a document approving the registration or requesting compliance with any requirement defined in the regulation.

The term of the members is three years and the renewal of registration must be requested each term. If there is a substitution of members at any time, this must be communicated to Conep, which maintains continuous dialogue with the CEPs through its coordinator and functions as the coordinating body of the system composed of the various institutional CEPs.

Each CEP must prepare and approve its Internal Regulation with the rules operating.

The existence of a CEP in the institution qualifies it and legitimizes its vocation for the search.

2.1 The choice of CEP members

According to Res. CNS n.º 196/96, the CEP must be constituted by a collegiate with no less than seven members. It must be multidisciplinary, multiprofessional, with professionals in the area of Health, Exact, Social and Human Sciences, including, for example, jurists, theologians, sociologists, philosophers, people who are dedicated to the study of bioethics and at least one member representing the users of the institution. There must be a balanced distribution of gender (men and women) in its composition, and it should not have more than half of its members belonging to the same professional category.

Participation is voluntary; the ways in which half of its research-experienced members are elected by peers and the choice of other members will depend on the institution's norms. In any case, the process must be transparent and clearly disclosed, in order to obtain the necessary legitimacy for the CEP so that there is due respect for its decisions.

People from outside the institution can be invited, with a profile that contributes to achieving the recommended multidisciplinary character (for example, for health institutions, external members can be jurists, theologians, sociologists, philosophers, bioethicists, people from the area of human rights, etc.) in addition to the user representative, to participate as full members. For special situations, *ad hoc* consultants may be invited whenever necessary.

It is recommended that CEP members declare their institutional and extra-institutional links, including their relationships with the pharmaceutical industry, whether as a researcher, consultant, speaker, shareholder or others that may imply a conflict of interest.

The term of office (three years, allowing for renewal) is set out in Res. CNS 196/96. The choice of the CEP coordinator must be made by its members and the method of choice must be clearly explained in the Internal Regulations.

The composition and procedures for decision-making in the CEP must ensure its fundamental characteristic of independence from political, institutional, hierarchical, corporate, financial and economic-market influences.

2.2 User Representatives

The presence of a representative(s) of the user(s) is essential so that the CEP can have the expression (the opinion) of the one(s) who use the institution's services or who most frequently can participate in projects as volunteers.

Among the methods for choosing user representatives, a referral to the Municipal Health Council or user associations already established and in contact with the institution can be requested, in addition to other related civil society associations, such as associations of patients with pathologies, associations of residents, associations of women, the elderly, etc. (see CNS Res. No. 240/97).

The user representative must not be an employee of the institution, nor assume a professional character; for example, for CEPs in the Health area, it should not be a health professional. In any case, it must be a person interested in the

study of ethics in research and in the defense of the rights of citizens and service users, being able to contribute to the discussions of specific protocols, representing the interests and concerns of the community and local society.

2.3 Initial training of CEP members

The minimum initial training must include:

- reading the CNS Resolutions on research ethics, the CEP Internal Regulations and this manual;
- discussion on the importance of CEPs to protect the dignity and rights of research subjects and to contribute to the development of relevant research, also emphasizing the educational role for researchers;
- obtaining indication of literature and electronic addresses of interest, including the Conep *website* (http://conselho.saude.gov.br);
- participation in discussions or presentations on national and international standards relevant to research involving human beings.

2.4 Promotion of continuing education for CEP members

The CEP should hold seminars, at least annually, to discuss the various ethical aspects of research. In addition, the use of electronic means (website, discussion groups, dissemination of bibliographies) should be encouraged to exchange experiences between members of different CEPs and Coneps, in addition to obtaining and reading updated bibliography on the subject. Finally, it should be remembered that the ongoing activity of protocol evaluation is the best means of continuing education for the members of a CEP. The study of the ethical aspects and dilemmas most frequently identified favors the deepening of the theme and should be the specific agenda of the meetings.

It is, therefore, essential to look for ways to value, encourage and finance the continuing education of members for a better appreciation of research protocols by the CEPs, preparing current and future members, including through programs of the courses of undergraduate and postgraduate courses.

2.5 CEP maintenance and financing

Institutional involvement is a precondition for the establishment and maintenance of the CEP. The importance of the CEP for carrying out ethically and scientifically correct and relevant research is indisputable. In this way, the members of the institution interested in its scientific and technological development have one more responsibility, that is, to clarify to the directors not only in relation to the

importance of the establishment of the CEP, but mainly of its importance for the institution, its researchers and users.

The Res. CNS No. 196/96 establishes that the organization and provision of the CEP's operating conditions are the responsibility of the institution, as part of the necessary infrastructure for carrying out research (organized services, records and files, stable human resources, laboratories, CEP in regular operation, etc.). Its funding must come from the specific budget of the institution, as is the case, for example, with scientific, undergraduate and graduate committees.

CEP funding models can be defined according to each institution. One of them would be for the institution to manage the budgets of all research carried out within its scope, discussing with the sponsor and researcher the allocation of resources, including those necessary for structural support to the CEP. Another model would be for the institution to require the inclusion of resources for its institutional development plan in the budget of each privately sponsored research project. What cannot occur is the charge for the assessment and issuance of an opinion.

It should also be noted that item III.3.s of Res. CNS 196/96 states that an important secondary objective of collaborative research is to help develop the capacity of the host country and institutions to independently carry out similar research projects, including their ethical evaluation.

The institution must find ways of encouraging and recognizing the voluntary participation of members in the CEP, establishing a specific workload, scoring for evaluation of academic productivity or functional progression, reimbursement of expenses with meals, transportation and others as needed.

3 Conducting a CEP Meeting

The CEP coordinator or, in his/her absence, a member chosen by the group must open, coordinate and close the meetings. The coordinator, in possession of the content, complexity and volume of work to be performed, chooses the best way of working for that session. Consensus should be sought, facilitating the analysis and debate by the group of all the arguments put forward.

The protocols must be presented to the collegiate by the rapporteurs, in such a way that the points described by the researcher are placed faithfully, avoiding inferences. If the procedures are not explained or give rise to doubts, the project must be pending, requesting clarifications. The coordinator must make sure that everyone can give an opinion and may use the expedient of passing the floor to another member of the collegiate in order to allow for discussions. Often, there is a need to set time limits and request precision in the exposition of ideas, as certain subjective nuances can lead to innocuous discussions.

Finally, lead the presentation and discussion of adverse events from studies involving new drugs/vaccines, protocol amendments, consultations and other demands to the CEP.

The idea of working with two or more rapporteurs can be interesting, as it makes possible the exchange, the learning, the desirable pluralism obtained with different points of view and the division of responsibilities. Project reporting must follow a rotation system, so as not to overload certain CEP members. Whenever possible, responses to pending issues on a project should be forwarded to the rapporteur responsible for its initial consideration.

Correspondence, participation in congresses, publication of new documents and educational material received should be shared, thus encouraging all members to exchange information and make their contributions to the group. Whenever possible, ask the collegiate for suggestions for drawing up the agenda for the next meeting, so that the work is progressively more and more integrated.

Other ways of operationalization that meet the profile of a given Institution can be defined and contemplated in the Internal Regulations of the CEP.

The active participation of user representatives should be encouraged, making them really feel part of a collegiate body, showing that their

opinions can be equally appreciated by the other members of the Committee; they can even be in charge of reporting protocols.

3.1 Role of the coordinator

Reviewing ethical aspects of a research protocol is a delicate task and one of great responsibility, as the CEP must thoroughly assess the facts and their consequences, as co-responsible for the project, being required to find the fine divide between fully justifiable and those in conflict with the principles of ethics. This requires flexibility to contemplate the different contexts and a rigorous process of reflection, solid and rational, in a fair and competent action, considering the interests of all involved.

In this scenario, in case of extreme complexity, the coordinator can act as a moderator in the discussions, identifying opposing opinions. It is up to him to allow the presentation of the pros and cons of the situation, encourage questioning, facilitate the group's conclusion and submit the decision in plenary. It is important to emphasize that the main decision is made by the collegiate, which will consider all the arguments presented.

It is also up to the coordinator to ensure compliance with the requirements of Conep/MS in accordance with CNS Resolution No. 196/96 and its complementary ones, to take cognizance of all research protocols to be analyzed and to arrange for their distribution on a rotating basis to the rapporteurs , ensure compliance with the deadlines and sign the opinions of the CEP on behalf of the collegiate, in addition to issuing other documents that may be necessary.

Finally, it is up to the coordinator to encourage the continuous improvement of CEP members in research ethics or even to designate members with the responsibility of taking care of this task in a special way.

3.2 Minimum quorum to meet and to deliberate

The CEP meetings must be attended by more than half of the collegiate to deliberate and/or approve research protocols.

If there is no minimum quorum, it is always an opportunity for the members present to take advantage of the time to exchange information, study and reflect on topics related to ethics in research and bioethics.

Any member of the CEP directly involved in the project under analysis must be absent during the evaluation, to avoid judgments under conflict of interest.

3.3 Drafting and approval of minutes

All matters dealt with must be clearly noted; record the presentation of the analysis of new protocols and responses to pending issues. The participation of an *ad hoc member,* if any, must also be recorded ; approval, pending or non-approval by the plenary; the analysis of adverse events related to research projects in progress at the Institution; other matters dealt with and decisions, as they will sometimes constitute guides or beacons for future deliberations. Also record the distribution of new projects, when it occurs, and responses to pending issues forwarded to reporters. Likewise, the name of all members present at that meeting must be included.

In the period between the CEP meetings, the notes will be reviewed and a draft of the minutes must be prepared to be distributed to the collegiate with the call for the next plenary meeting.

4 The Rapporteur's Role

The rapporteur is a member of the Research Ethics Committee who is tasked with studying a question or analyzing a research protocol and presenting to his colleagues a report that allows for a broad discussion of the ethical and methodological aspects involved and decision-making. by the collegiate.

It is important to point out that the rapporteur is at the service of the CEP. Although acting with autonomy and independence in the elaboration of its opinion, the final decision is taken collectively by the Committee. The rapporteur, when reading, analyzing and presenting his opinion on the research protocol, provides an important service to the researcher, the Research Ethics Committee, the institution, Conep and society, exercising social control of research ethics, as provided for in the SUS guidelines.

This analysis consists of highlighting what is good about the protocol and why it is good; in pointing out ethical flaws in the protocol, with the reasons why they are considered flaws; to facilitate the Committee's discussion of the ethical merits of the research project in question; in helping the CEP to approve or disallow the proposed research, basing this decision on ethical criteria and on the norms contained in the CNS Resolutions and others, as the case may be.

The embodied opinion is an instrument that allows the rapporteur to organize in a succinct manner his understanding of the research objectives, his appreciation of the ethical issues raised by the research proposal and his reasons for considering the project ethically acceptable or not.

The rapporteur has a double task: the technical task of reading the project and preparing the opinion, and the ethical task of reflecting on ethical values and counter-values. The embodied opinion seeks to communicate, for those who have not read the project, its main points, make clear the ethical elements that appear in the project and allow a fair judgment on the ethical merits of the project.

The rapporteur is a defender of human dignity: he defends the human dignity of the research subject, the human dignity of the researcher and the interests of society.

Some fears that arise in relation to the rapporteur and his work can be mentioned: that the rapporteur acts as a police figure, more interested in finding flaws in the protocol than its merits; that attention to bureaucratic details undermines an innovative and creative research proposal; that a reporter from another area of knowledge does not have the competence to appreciate a protocol and assess the risks and benefits for the research subjects.

It is important that the CEP coordinator and the rapporteurs themselves take the necessary measures to ensure that these fears are unfounded. When

where applicable, the rapporteur will supplement his information with readings and consultations on the methodological and technical aspects that raise doubts, in order to be able to discuss the ethical issue more safely. Furthermore, all CEP members, contributing with their specific competence and exercising their own responsibility, will most certainly construct an adequate final opinion. It will be up to the CEP whether or not to accept the opinion of the rapporteurs, with the necessary amendments. The CEP must treat the distribution of projects to the rapporteurs as confidential, who will present their specifically embodied opinion to the Committee.

Eventually, when a project presents particularly complex problems, whether of a technical or ethical nature, another rapporteur can be appointed among the members of the CEP or an *ad hoc rapporteur,* therefore a consultant not belonging to the CEP, with technical competence and/or or special ethics to appreciate the case. You can also turn to Conep, explaining the specific reasons and dilemmas.

5 *Ad Hoc* Consultant Role

The *ad hoc* consultant is the one who, not participating in the Committee, is invited to give its opinion to advise the CEP.

Seeking the expression of an *ad hoc* consultant can have a number of functions: helping to guarantee the pluralism of the CEP, guaranteeing technical or specialized competence, and promoting justice and equity in decision-making.

The concern with pluralism and technical or specialized competence is manifested in Res. CNS No. 196/96, in item VII.5, when it insists that the Research Ethics Committee must have a multi and transdisciplinary character. Also, in this context, it states that “It may (...) count on *ad hoc* consultants , people belonging or not to the institution, with the purpose of providing technical subsidies”.

The issue of justice appears in item VII.6 of Res. CNS n.º 196/96, which talks about research in vulnerable groups, communities and collectivities. In these cases, “a representative of the group should be invited, as an *ad hoc* member of the CEP, to participate in the analysis of the specific project”.

It is good practice to explain to the *ad hoc* consultant the aspects on which its manifestation is required, also clarifying that it will be submitted to the Committee. It will be up to the CEP to accept or not the *ad hoc* consultant's opinion and to be responsible for the final decision. Therefore, neither the rapporteurs who are members of the Committee nor the *ad hoc* consultants should have their identification disclosed outside the Committee.

6 Relationship between the CEP and the Researcher

The various national and international forums aimed at the development of research and the guarantee and applicability of human rights have pointed to a closer, cooperative and mutual trust work between the CEP and the researcher.

The researcher must be received at the CEP secretariat by an administrative employee or by any member of the CEP who can expose their *modus operandi,* which protocols will be assessed only at the Institutional CEP and which, after the CEP has been assessed, must be forwarded to Conep, flows and deadlines, providing the necessary resolutions and forms.

The relationship must be transparent, objective and welcoming. The members of the Research Ethics Committee can assist the researcher in his/her doubts, suggesting certain points to be highlighted in the body of the project (eg return of benefits to the researched community, incorporation of new technologies and a way to ensure continuity of treatments, analysis of risks and benefits, justification for placebo, etc.) or in the use of more appropriate language for the Free and Informed Consent Term.

The CEP should seek to assist and provide guidance to researchers even before the protocol is presented, and may assist the researcher in the design and in some other aspects, such as the process of obtaining consent.

After the issuance of the approval document by the CEP/Conep, it is worth reminding the researcher responsible for the project, the commitment to send partial and/or total reports of their research to the CEP, informing the progress of the same, also communicating adverse events and eventual changes in the protocol.

The researcher is the CEP's interlocutor, the liaison with the sponsor and other involved in the research, including the research subject.

7 Projects that must be presented to the CEP and who must do it

The Res. CNS No. 196/96, item II.2, considers research on human beings to be carried out in any area of knowledge and that, directly or indirectly, involve individuals or collectivities, in their entirety or parts, including the management of information and materials. See also the definition of search, in that resolution. Thus, research involving human beings is also considered to be interviews, application of questionnaires, use of databases and review of medical records. Some evaluation projects are not characterized as research.
Whenever there is doubt, it is recommended that the protocol be presented to the CEP, which will make the decision on the specific situation.

It should also be noted that it is not the proposals for lines of research that should go to the CEP, but the specific projects, with their respective protocols, to be developed within these lines or programs.

A researcher responsible for the CEP and the institution must correspond to every research protocol, even if it is carried out by a team.
In multicenter projects, there must be a responsible researcher at each location where the research will be carried out. It is responsible for coordinating and carrying out the study, ensuring the integrity and well-being of the researched people (subjects of the research), submitting the protocol to the CEP's consideration, sending reports on the progress of the research and the final report upon its completion, being responsible for thereby the legal and techno-scientific responsibility of the study.

The submission of the protocol to a CEP does not depend on the level of research, whether a work for the conclusion of an undergraduate course, whether of scientific initiation or a doctorate, is of academic or operational interest, provided that it is within the definition of “research involving human beings”.

Postgraduate studies presuppose the existence of professional responsibility, the development of competences in the scientific and methodological areas and the researcher's knowledge of the norms for the protection of research subjects. Therefore, the graduate student is qualified to assume the role of responsible researcher.

On the other hand, the participation of undergraduate students in research presupposes the guidance of a professor responsible for the undergraduate student's activities and, therefore, the guiding professor must appear as a responsible researcher.

8 Receipt of a Research Protocol at the CEP

The CEP should only receive research protocols properly prepared in Portuguese. This means that they must contain all documents and information listed in item VI – Research Protocol – CNS Resolution No. 196/96 and other specific documents, in accordance with the complementary rules for special thematic areas.

In order to speed up the processing of the research protocol, it is interesting that the administrative agent of the CEP, upon receiving it, checks if it is complete. For this, you can use the checklist, the form **"Documents necessary for analysis of the research project"** prepared by Conep (attachment), marking the items corresponding to the documents presented. The documents to be delivered to the CEP include, in addition to the research project itself, others absolutely necessary for the ethical evaluation, marked on the list. The set: research project plus other required documents, is called a research protocol.

In case of absence of essential documents or information, the protocol should not be received before the responsible researcher completes what is necessary. Thus, incomplete research protocols should not be received and appreciated by the CEP, with the exception of the CEP approval document from the country of origin, when protocol evaluations are carried out simultaneously in the country of origin and in Brazil. In these cases, the protocols can be evaluated, with the start of the research being conditioned to the presentation of approval in the country of origin.

The formalization of receipt of the protocol by the CEP is also necessary. A mechanism to protocol the received document must be created by the CEP, for the security of both parties (researcher and CEP). From the moment a research protocol enters the CEP to be assessed, it must receive a number, which will correspond to its identification.

Once the complete research protocol has been received, the CEP must forward it for consideration by at least one reporter. Many institutions refer it to two rapporteurs and others to all members. It is worth noting that it is not necessary to wait for a meeting to distribute the report.

These guidelines seek to streamline the procedures related to the receipt of the research protocol at the CEP, its processing and, consequently, to speed up its appreciation.

9 Research Protocol Evaluation

9.1 Documents that must compose the protocol and the reasons for your request

(see Res. CNS no. 196/96 – VI – and resolutions on thematic areas)

The research protocol must be delivered to the CEP in two or three copies, with a cover letter, in addition to the identification of the main researcher and confirmation of knowledge of its content signed by all researchers. The three-way requirement is justified because a copy is kept by the CEP up to five years after the project is completed and one or two others will be forwarded to the rapporteurs. In case of a project in a special thematic area, two copies must be sent to Conep. It is important to emphasize that the rapporteurs must return the protocols to the CEP, after their final assessment, and these same copies may be sent to Conep, if applicable.

The first document is the Face Sheet, made available by Conep on the *home page,* with the term of commitment of the researcher and the institution to comply with Res. CNS no. 196/96 (VI.1 and VI.5). This is the document that gives legal consistency to the project, because it identifies the responsible researcher, the institution and the CEP, who must sign their signatures, and are committed to complying with the rules and the corresponding responsibilities. The institution's commitment must be signed by the legal representative (director, president, etc.). The project title cannot contain strikethroughs. Abbreviations, symbols and/or figurative elements should be avoided, as the information is essential to compose the project database. In addition, it contains data on the main characteristics of the research, allowing its classification according to some risk criteria and the definition of the evaluation flow. Therefore, all data must be correctly filled in.

The second document is the research project itself, in Portuguese. The need for this document is obvious, because it is through it that the ethical analysis will be carried out and the methodological adequacy will be verified. It is important to emphasize that, although the adequacy is not made by the CEP, but its evaluation, the methodological soundness is itself an ethical issue. A research project with serious methodological flaws is necessarily ethically flawed as well. The research project must include, at a minimum, what is required by Res. CNS No. 196/96, VI.2 and VI.3.

The third document, one of the most important, is the Free and Informed Consent Term – TCLE (Res. CNS No. 196/96-VI.3.e), prepared by the researcher in a language accessible to the understanding of the research subjects. This document explicitly demonstrates the recognition of the research subject as an autonomous being and the best defender of their interests. The protection of research subjects is the fundamental reason for the Brazilian Norms and Guidelines that order research involving human beings, including Res. CNS No. 196/96.

The TCLE, although sensitive to the position of the researcher, the institution, the promoter and the sponsor, aims to protect, in the first place, the research subject. Therefore, it should never have the connotation of "disclaimer".
By protecting the research subject, the researcher and others involved are indirectly protected, including the CEP, which becomes co-responsible for the research after its approval. The informed consent must be obtained after the research subject and/or his/her legal guardian is sufficiently informed of all possible benefits, risks and procedures that will be performed and all information relevant to the research is provided.

It is also extremely important that the process for obtaining the TCLE is described.

The signature of the term by the research subject or their legal guardian must also confirm their knowledge of the access routes to the researcher and/or the institution (phone numbers and addresses), in the event of emergencies related to the development of the research. In some cases, it is recommended that the forms of quick access to the CEP also be included for situations not resolved by the researcher.

There are special situations (Res. CNS No. 196/96-IV.3.c) in which the Free and Informed Consent Form can be waived, and must be replaced by a justification with the reasons for the impossibility of obtaining it. This justification must be presented in attached documents, as is the TCLE, and the CEP will judge its relevance.

In case the research foresees the use of stored biological material, originating from other researches or obtained by routine procedure in the practice of services, an informed consent should be obtained, as far as possible, for each new study purpose. If this is not possible, the person responsible for the institution that has custody of the material must consent or not to the material being used, safeguarding the interests of the material donors, their image and their privacy, among others. Approval of the project must come from the institution's CEP. Every new use in research must be formalized in a project and submitted to the CEP.

It is interesting to recall the distinction between databases and biological material that already existed before Res. CNS n.º 196/96 and that were formed without the consent of the material donors and those established from the Resolution. Specific informed consent is required for each new research and a generic consent is not considered sufficient. For this reason, databases where future research is planned must have built-in mechanisms to update donor consent when a new research proposal arises. In special cases, justification for the impossibility of obtaining the TCLE must be attached to the project for deliberation by the CEP.

In surveys carried out through the application of questionnaires, the Free and Informed Consent Term must guarantee the research subject the right to refuse to answer questions that cause embarrassment of any nature and it is important that the CEP is aware of the questionnaires that will be used, as sometimes modifications are necessary in order to make the research instrument more ethically appropriate and less invasive to the individual's privacy. It is not up to the CEP to make changes to the proposed instruments, but, in the event of an ethical problem, to provide guidance on the necessary points.

In cases where there is any restriction on freedom or on the clarification necessary for adequate consent, or when there is a relationship of dependence of the subjects vis-à-vis the researcher, article IV.3 of Res. CNS No. 196/96.

The fourth document required is the detailed budget of the research project: resources, sources and destination, as well as the form and amount of the researcher's remuneration (Res. CNS n.º 196/96-VI.2.j).

There are some important considerations to make regarding this document. ment, which justify their request, from an administrative and ethical point of view.

From an administrative point of view, several issues must be checked:

1) no examination or procedure performed solely for the purpose of research can be charged to the patient or to the agent paying for their assistance, and the research sponsor must cover such expenses;
2) the establishment of payments for these procedures, in the case of external sponsors, must be agreed between the sponsor and the institution;
3) the institution must be aware of the research and its repercussions budgetary statements.

From an ethical point of view, other precautions should be taken:

1) the researcher's payment can never be such that it induces him to change the risk/benefit ratio for the research subjects. Discourage it being based solely on the number of volunteers recruited;
2) there should be no payment to the research subject for his/her participation. Only the reimbursement of expenses necessary for its follow-up is allowed (Res. CNS n.º 196/96, VI.3h), for example expenses with tickets and food;
3) double payment for procedures cannot occur, especially involving unauthorized public expenditures (SUS).

The fifth document is the *curriculum vitae* of the main researcher and the other participating researchers (Res. CNS no. 196/96-VI.4). The reference to “Curriculum Lattes”, together with the CNPq, may be sufficient. The main rationale for requesting this document is for the assessment of technical capacity and suitability.

ethical status of the researcher to carry out that research. This does not mean that the researcher has already carried out similar research, but only that he has the technical capacity to carry it out.

If the research is conducted abroad or with foreign participation, a document of approval of the study by the Research Ethics Committee or equivalent in the country of origin is required (Res. CNS No. 292/99-VII.1 and 2) , proving the acceptance of the study to be carried out in that country. If the study is not planned to be carried out in the country of origin, the justification for not carrying out the research and for choosing the collaborating country must be presented.

In multicenter studies, the list of centers and researchers involved should be included.

If the research is carried out in a health institution, the technical person in charge must be aware of and agree to its execution, by signing the Term of Commitment on the cover page, since he is responsible for all acts carried out in the institution. .

9.2 Evaluation of scientific methodology

(see Res. CNS n.º 196/96-III.3.aee)

There are certainly several models for evaluating the design and methodology. Why evaluate project design and methodology?

According to item VII.14, of Res. CNS n.º l96/96, the ethical review of any and all research involving human beings cannot be dissociated from its scientific analysis. It is not justified to subject human beings to risks unnecessarily and all research involving human beings involves risk (Res. CNS no.
196/96-V). If the research design is methodologically inappropriate, it is useless and ethically unacceptable.

This evaluation by the CEP can sometimes be difficult. In these cases, *ad hoc* consultants can be used or, as many institutions do, create specific Scientific Committees for this task, only forwarding the research protocol for ethical evaluation after its methodological approval, which, however, does not exclude the responsibility of the CEP for approval. integral part of the research protocol.

9.3 Risk and benefit assessment

(see CNS Res. No. 196/96-V)

Assessing the risks and benefits that can be anticipated involves a series of steps.

The CEP must:

1) identify the risks associated with the research and differentiate them from those that the subjects would be exposed to through care procedures;
2) verify if the necessary measures have been taken to minimize the foreseeable risks (considering the physical, psychological, moral, intellectual, social, cultural or spiritual dimensions, according to item II.8, of Res. CNS n.º 196/96);
3) identify the likely benefits that may arise from the research;
4) verify that the risks are in a reasonable proportion in relation to the benefits for the research subjects;
5) ensure that potential subjects receive an adequate and accurate description and information of the risks, discomforts or benefits that may be anticipated;
6) determine intervals of periodical reports to be presented by the researcher and, when applicable, that the researchers make available to the CEP the data necessary for monitoring the project.

9.4 Analysis of the Free and Informed Consent Form (TCLE)

(see CNS Res. No. 196/96-IV)

Often, the rapporteurs start the analysis of the research protocol by the TCLE, as it is one of the most important documents and because it should provide a complete understanding of the project and its implications for the research subjects. If the reporter has doubts, the ICF was certainly not well written by the researcher. There are some fundamental points in its construction: it must be written in accessible language and it must contemplate all the requirements of Res. CNS No. 196/96, IV, IV.1 and IV.2, including the researcher's address and telephone number for contact in case of need.

It is necessary to verify if the signature or copy printing is foreseen by each and every one of the research subjects or their legal representative and by the researcher, and if the Consent Term will be prepared in two copies, one with the research subject and the other filed by the researcher. In the event that there is any restriction on freedom or on the clarification necessary for adequate consent, the provisions of Res. CNS No. 196/96, IV.3.a,b,c,d,ee f.

When research projects are carried out with minors in day care centers, schools, etc., it is up to the legal representatives of the subjects (family member, tutor)

have knowledge and sign the Free and Informed Consent Term. However, the subject's own consent, even if in a situation of limited competence for autonomous decisions, must be obtained. Those responsible for the institutions (schools, day care centers, etc.) do not have the authority to give or sign the TCLE, but must sign a document authorizing contact with the subjects, assuming the responsibilities.

9.5 Assessment of the process for obtaining Consent

The CEP should emphasize the importance of the free and informed consent process and not only the signing of the Consent Term, which should only be obtained after the research subject is sufficiently informed of all possible benefits and risks and all pertinent information has been provided. the search. If the subject is a patient at the service, it is advisable to record the procedures for the implementation of the free and informed consent process in the medical record, whenever possible.

Thus, the protocol must contain the description of the procedures for clarification of the subject (individual information, groups, lectures, videos, etc.) and by whom it will be done, verifying the need for the intervention of a person other than the researcher. Resources from the research budget may also be required to adequately carry out this stage.

The signature of the TCLE constitutes only a moment of the consent process and not necessarily the final moment, since all consent, in addition to being free and informed, is also renewable and revocable.

9.6 Adequacy of information related to the research subject and inclusion and exclusion criteria

Defining an appropriate group of subjects for a research project involves a variety of factors, including: vulnerability, competence to decide participation, scientific design needs, susceptibility to risks, possibilities of benefits, practicality and fairness considerations.

The research protocol must describe the characteristics of the population to be studied, including sample size, age group of subjects, gender, ethnic group, general health status, social groups and explain the reasons for using vulnerable groups. It should also, where applicable, describe the plans for recruiting individuals and the procedures to be followed.

The CEPs must analyze whether, in the selection of subjects, equity and fair distribution of burdens and benefits are respected.

Points to consider in the inclusion and exclusion criteria:

1) Do the risks or discomforts resulting from participation in the research fall on the subjects who are likely to have the greatest benefits from the research?
2) Did the recruitment of subjects avoid placing a disproportionate amount of research risks or discomforts on a particular group of subjects?
3) Is there any population group that could be more susceptible to the risks presented by the study and that could therefore be excluded from the project? Are the procedures for identifying such a group adequate?
4) Are the expected benefits for the subjects distributed impartially? Is there another group of potential subjects who need these benefits more?
5) Is there the inclusion of groups of vulnerable subjects and why is their inclusion justified? Is there a possibility of conducting the research with some less vulnerable group? What kind of costs or inconveniences would such an attitude bring?
6) Did the selection remove subjects considered vulnerable, such as children, pregnant women, people with reduced autonomy, poor people or people with little education, very sick patients, so that they would lose the opportunity to participate in research and enjoy the benefits arising from them?
7) And the subjects are susceptible to pressures (dependency situations such as recruitment of employees, students, military, etc.). Are there mechanisms to minimize pressures or reduce their impact?

9.7 Privacy and confidentiality

Privacy derives from autonomy and encompasses the intimacy of private life, the honor of people, meaning that the person has the right to limit the exposure of their body, their image, data from medical records, judgments expressed in questionnaires, etc. Confidentiality refers to the responsibility for the information received or obtained in examinations and observations by the researcher in relation to the research subject's personal data. Both must be explicitly guaranteed in the research protocol and in the TCLE (Res. CNS No. 196/96, IV.1.g) and the research subject must be assured that personal data arising from participation in the research will be used only for the purposes proposed in the protocol (Res. CNS no. 196/96 IV.3.f).

Many health institutions establish internal rules for the use of data from medical records and databases in research projects, taking into account

based on Res. CNS No. 196/96-III.3.i (provide for procedures that ensure confidentiality and privacy, image protection and non-stigmatization, ensuring that information is not used to the detriment of people and/or communities, including in terms of self-esteem, prestige and/or economic and financial) and item III.3.t (use the biological material and data obtained in the research exclusively for the purpose provided for in its protocol). The researcher must establish secure safeguards for the confidentiality of research data. Participating individuals should be informed of the limits of the researcher's ability to safeguard confidentiality and of the possible consequences of breaching confidentiality. When research involves institutional data, privacy and confidentiality must likewise be preserved (eg organizational research in psychology or administration).

9.8 Evaluation of the Free and Informed Consent Form in surveys carried out through the application of questionnaires

The ICF must guarantee the individual the right to refuse to answer questions that cause embarrassment of any kind. It is important that the CEPs are aware of the questionnaires that will be used in the surveys.

In some cases, the TCLE may or even should not be identified, in situations in which the anonymity of the research subject must be maintained, for example, when activities considered illegal are identified. In surveys with an anonymous questionnaire, the fact of answering the questionnaire would be considered as consent and the procedures for the due clarification of the subjects must be described for the appreciation of the CEP.

To facilitate the analysis of item 9 discussed here, Conep prepared a checklist (Annex 2).

10 Preparation of the Embodied Opinion

(see CNS Res. No. 196/96-VII.13.b)

The CEP must issue the Consubstantiated Opinion in writing, within a maximum period of 30 (thirty) days after receiving the research protocol, after careful analysis by the rapporteur(s) and appreciation by the CEP. An ethical analysis must be carried out, identifying the critical points of the project and, through the terminology of bioethics and ethics in research, analyzing risks, benefits and equity in their distribution, equity in the recruitment of research subjects and respect for their autonomy.

The Final Opinion must also clarify the need to present partial and final reports, specifying the expected dates, the notification of adverse events and any amendments or modifications to the protocol, for the CEP's consideration. In addition, in the cases provided for in the rules, the referral to Conep must be mentioned, explaining that the research can only be started after receiving approval from Conep.

The CEP's Substantiated Opinion must be incorporated into the Protocol. Pay attention to the inclusion of all possible changes made, for example, including the researcher's clarifications, new informed consent, if applicable, with the date and specification that it is the approved version.

As defined in Res. CNS No. 196/96, opinions must be “approved”; “approved with recommendation” – when the requirement to be met is not an impediment to the start of the research; “pending” (does not mean approved) – when prior approval and initiation of the research are required, and, finally, “not approved” – when there is an ethically incorrect, unacceptable issue in the protocol. In this case, there is no alternative, the researcher could present another protocol.

The CEP's substantiated opinion is the result of the Committee's discussion and deliberation, and must be signed by the Coordinator, demonstrating that it is the opinion approved by the CEP and not just the report of the rapporteur, whose identification must not be disclosed externally to the CEP.

11 Amendments and Extensions: what they are and how must process

Amendment is any proposed modification to the original project, presented with the justification that motivated it. Extension is the proposal to extend or continue the research with the same recruited subjects, without essential changes in the objectives and methodology of the original project. If there are important changes in objectives and methods, another research protocol must be presented.

Request that the amendments be presented to the CEP in a clear and concise manner, identifying the part of the protocol to be modified and its justifications. In case of projects of group I or II previously submitted to Anvisa, the researcher or sponsor must also send them to Anvisa together with the CEP's approval report, to be added to the original project. There is no need for Conep's opinion, both for amendments and extensions (as defined herein), unless the CEP requests it because it identifies a specific dilemma. It is worth remembering the provisions of Res. CNS No. 251/97, item III.2.e.

12 The Need to Order Documents and Create a File

The requirement of complete documentation, as described in Res. CNS n.º 196/96, is indispensable not only to enable the analysis of research projects by the CEP, but also to legitimize their execution.

The main objective of this requirement is to ensure the protection of research subjects. In addition, it serves as a guarantee for the researcher responsible for the project, as well as for the research institution where it is carried out and also for the CEP and Conep, when applicable, because the ethics committees are co-responsible for the approved projects.

Incomplete documentation, in addition to making it difficult or even impossible to ethical analysis, can even cause legal problems.

It is essential to install the file in a suitable location, with corresponding to the volume of projects analyzed by the CEP.

All documents referring to the research protocols analyzed by the CEP must be archived for a minimum period of 5 (five) years after the end of the study. They must be available for eventual consultation by Conep and by health surveillance agencies.

All documents referring to the analyzed processes must be filed: complete research protocol, Free and Informed Consent Term (ICF), researchers' curricula, terms of commitment of the Institution, opinions issued by CEP members, *ad hoc* consultants
and all opinions emanating from the CEP, addenda and modifications to the protocol as well as the TCLE, correspondence sent and received regarding the research project, in addition to progress reports, final report and publication of results, when available.

Projects should be readily available for consultation during CEP meetings. The confidentiality of the information contained in the archived documents must also be guaranteed, obtaining a commitment to secrecy on the part of the employees.

13 Follow-up of Research Protocols After Your CEP Approval

The CEP's responsibility does not end with the approval of the research protocol by it or by Conep (in the case of projects related to special thematic areas). On the contrary, from then on, the CEP becomes co-responsible for the ethical aspects of the research. It is your duty to monitor and ensure that the research is carried out in the way it was approved.

It is the responsibility of the CEP to request reports from researchers. According to item VII.13.d, of CNS Resolution No. 196/96, such reports must be annual (partial or final, depending on the duration of the research). In the works on “Drugs, medicines, vaccines and diagnostic tests that are new or not registered in the country” (special thematic area number 03), the reports must be biannual (CNS Resolution No. 251/97, item V.1.c) .

Once the protocols are approved, the dates for requesting their respective reports should already be determined and explained to the researcher in the opinion, in addition to being recorded on the protocol cover sheet.

The CEP may, to facilitate the analysis and direct the information it deems necessary, prepare a “Report Form” to be filled in by the researcher, containing questions not only referring to scientific aspects, but especially to the ethical aspects of carrying out the work.

It is also up to the CEP, according to items VII.13.feg, of CNS Resolution No. 196/96, “to receive from the research subjects or from any other party reports of abuses (...) deciding to continue, modify or suspension of the research (...)”, and “require the institution of an investigation to the direction of the institution in case of denunciation of irregularities of an ethical nature in the research (...)”. Item V.1.e, of CNS Resolution No. 251/97 also allows you to “summon research subjects for monitoring and evaluation”.

Thus, the monitoring of research protocols is vital and occurs routinely and regularly through the request of reports. However, at any time, if relevant, the CEP may request clarification on the development of the research.

The follow-up of the research is also done through the consideration of eventual amendments to the protocol and the reports of serious adverse events that have occurred.

Upon receiving a notification about the occurrence of serious adverse events, the CEP must assess the conduct taken by the researcher regarding the safety of the subjects involved and give its opinion. If these behaviors are not

are explicit, ask the researcher for a position that answers the following questions:

- Has the service been properly forwarded to the person involved?
- Does the event point out new risks to other research subjects?
- What are the measures to be taken to protect the subjects? Is it necessary to add new forms of monitoring, examinations, follow-up visits or modify treatment regimens?
- Should the research continue or be suspended?
- Should all subjects become aware and have the chance to make a new decision to participate, through a new informed consent?
- Have arrangements been made for any necessary modification of the protocol and the TCLE (amendments), and presented to the CEP for consideration?

Even if the event did not occur in subjects from this center, it must be analyzed by the researcher and the CEP, considering the questions above, executing the first one.

It is the researcher's role to ensure adequate immediate measures in the event of a serious adverse event, and it is up to the CEP to assess this conduct and forward the notification along with its opinion to Conep. This will monitor the adequate implementation of protection measures for the subjects and will forward, to the National Health Surveillance Agency, notifications for pharmacovigilance actions and other pertinent ones.

Other forms of monitoring research have been used, such as, for example, the random choice of projects already approved, under development, to be evaluated and to verify compliance with the rules. It is up to the CEP to identify and adapt new forms.

In the event that the CEP becomes aware of non-approved research being carried out, according to item VII.13. g, from Res. CNS n.º 196/96, “requires the initiation of an investigation to the direction of the institution in case of denunciation of irregularities of an ethical nature in the research”. Research not yet approved or disapproved and in progress, configure ethical irregularities and, therefore, require investigation by the CEP.

14 What the CEP Should Forward to CONEP

The CEP must forward to Conep:

- copy of the research protocols that need to be analyzed (according to the rules and flowchart), complete, with any modifications requested by the CEP, preferably with the initialed pages, attaching its substantiated opinion;
- projects that end a situation on which there was no consensus and that, according to the CEP's criteria, Conep's manifestation is desired;
- notifications of serious adverse events, after consideration and opinion regarding the immediate measures taken by the researcher and other guidelines to the same;
- quarterly reports on the functioning of the CEP, including a spreadsheet with the number of projects analyzed, approved and not approved, according to the model published by Conep (available on the *home page),* accompanied by a copy of the Cover Sheets;
- the changes in the composition of the CEP with the replacement of members that took place, a new term of office and the election of a new collegiate or the choice of a new coordinator;
- specific consultations on ethics in research involving human beings, as well as suggestions for improvement and adequacy of the system and standards.

Correspondence related to research projects already presented to the Conep must make a clear reference to the Conep registration number.

Special attention should be given to the procedure for sending protocols for special thematic areas, with immediate measures after their consideration at the CEP to reduce transit time, defining who is responsible for immediate dispatch, preferably via mail - registered correspondence - or fast delivery .

It is not fair to increase the processing time of projects due to extended times for simple transit.

15 Relationship between zip codes

The relationship between CEPs can have several purposes, such as:

- the exchange of experiences and decision-making methods on project analysis;
- the use of members as *ad hoc* rapporteurs ;
- the involvement of committee participants with greater experience as external members in the collegiate bodies that are in their initial phase of operation;
- jointly carrying out activities of an educational nature: courses, seminars, lectures;
- participation in peer reviews or audits.

16 CEP Educational Activities

A fundamental role to be played by the Local Research Ethics Committee must be to promote initial training and continuing education for its members, as well as for researchers and research subjects involved with the institution of which it is a part.

When starting to participate in the CEP, all new members must receive introductory training on the historical evolution of research ethics, relevant national and international standards on research ethics, the Resolutions of the National Health Council and basic texts on the topic . In the CEPs where part of the collegiate is renewed, the remaining members will make the adaptation. In CEPs with full renewal, this adaptation will be done by the departing members, before the broadcast.

It is important that the CEP makes available to its members and to researchers, electronic addresses related to the topic of ethics in research, being always open to receive suggestions and incorporations from researchers.

The educational role can also be played by holding meetings, seminars, round tables, discussion groups, creating an electronic page *(website)* and other means that allow reflection and discussion of ethical issues, cases with specific dilemmas and conflicting situations. .

Basic courses on “ethics in research with human beings” should be encouraged for institutional researchers, undergraduate and graduate students and user representatives (due to the different forms of representation developed in the current social dynamics: civil associations, organizations non-governmental organizations, etc.).

If there are local conditions, the development of studies and research on related topics should also be encouraged. The activities must be oriented towards the observance of the ethical guidelines and norms proposed by the current resolutions.

The educational role can also be played by the CEP acting as a consulting body for the researchers during the elaboration of the research project, fundamentally in the elaboration of the “Free and Informed Consent Term” (some CEPs maintain an on-call person to guidelines), and eventually, to the research subjects, when there are doubts and questions about the adequate compliance with the current ethical norms and guidelines. This task does not end with the approval of the research project, but must be permanent in the development of projects.

17 What to Do When Resolutions and Other Texts Rules Are Not Clear and How to Handle Cases omitted

The Res. CNS n.º 196/96 and its complements are not and could not be a code, with strict rules. They contain guidelines that will guide the ethical judgment of the protocols and establish operational norms. Dilemmas identified in the protocols and not covered in the guidelines should be the object of reflection and decision by the CEP. The latter can also count on Conep, emphasizing its role as advisor and coordinator of the system, which can be consulted whenever the CEP considers it relevant, as foreseen when defining the special area 9, of Res. CNS No. 196/96 (at the discretion of the CEP). The researcher may also consult the CEP, when deemed necessary, and, eventually, Conep itself.

These consultations will also be subsidies for the elaboration of new directives. guidelines or recommendations and updating of current ones.

Conep is also responsible for acting as a resource instance when there are divergences or questions from any of the parties involved in the projects – CEPs, researchers, institutions, sponsors and research subjects (Res. n.º 196/96-VIII. 4.e).

18 What Should Be Included in the Bylaws

Once constituted, the first collegiate must prepare a document with its operating rules, approving an Internal Regulation. The bylaws must include, among others:

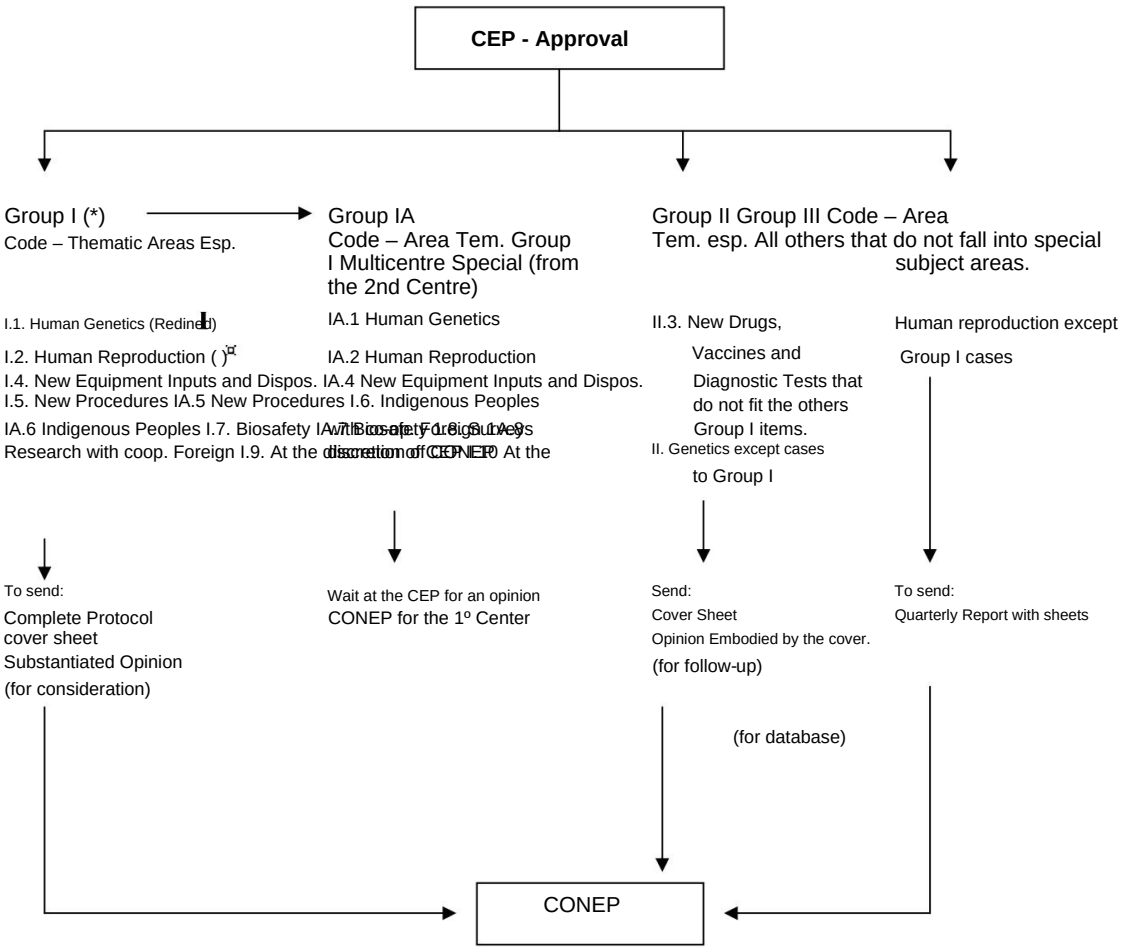
- CEP roles and responsibilities;
- its institutional link;
- their attributions;
- its constitution;
- its administrative structure;
- mechanisms for appointment, for renewal (must be partial to maintain the experience already accumulated while renewing), for exclusion (for example, for unexcused absences) and for replacements of members;

- member duties and responsibilities;
- minimum quorum for meetings and decisions;
- definition and role of *ad hoc members;*
- frequency of meetings;
- form and deadlines for submitting projects;
- methodology for evaluating, approving and monitoring research projects (stipulating deadlines for receipt and analysis, among others);

- general and transitional provisions.

It is worth remembering that several CEPs already established have their regulations available electronically, which may facilitate the preparation of internal rules for new CEPs (see *links* to the various CEPs on Conep's *home page).*

Annex A - Research Project Processing Flowchart Involving Human Beings, in accordance with the Resolutions of the National Health Council



(*) Only the 1st center of the multicenter Projects of Group I

( ) Resolution CNS nº 340, of July 8, 2004. Item VI, will send to CONEP (Group I) cases involving:

- Sending abroad genetic material or any human biological material to obtain material genetic;
- Storage of biological material or human genetic data abroad and in the country, when in agreement with foreign institutions or in commercial institutions; - Changes in the genetic structure of human cells for in vivo use; - Research in the area of genetics of human reproduction (reprogenetics); - Research in behavioral genetics; and - Research in which the irreversible dissociation of the research subjects' data is foreseen.

( ) CNS Resolution No. 303, of July 6, 2000. Item II, will send to CONEP (Group I) cases with intervention in: - Assisted reproduction; - Contraception; - Manipulation of Gametes, Pre-embryos, Embryos and Fetus; - Fetal Medicine.

Annex B - Cover Sheet

MINISTRY OF HEALTH
National Health Council
National Research Ethics Commission - CONEP

FOLHA DE ROSTO PARA PESQUISA ENVOLVENDO SERES HUMANOS (versão outubro/99)

1. Research project:			
2. Knowledge Area (See list on the back)		**3.** Code:	**4.** Level: (Knowledge areas only 4)
5. Special Thematic Area(s) (See flowchart on reverse side)		**6.** Code(s):	**7.** Phase: (Thematic area 3 only) I () II () III () IV ()
8. Uniterms: (3 options)			
SUJEITOS DA PESQUISA			
9. Number of subjects Not Center : Total:	**10.** Special Groups : <18 years ( ) Mentally Disabled ( ) Embryo/Fetus ( ) Dependency Relationship (Students, Military, Prisoners, etc.) ( ) Others ( ) Not applicable ( )		
PESQUISADOR RESPONSÁVEL			
11. Name:			
12. Identity:	**13.** CPF.:	**19.** Address (Street, no.):	
14. Nationality:	**15.** Profession:	**20.** POCKET:	**21.** City: **22.** U.F.
16. Highest Degree:	**17.** Position	**23.** Phone :	**24.** Fax
18. Institution to which it belongs:			**25.** *Email:*

Termo de Compromisso: I declare that I know and will comply with the requirements of Res. CNS 196/96 and its complements. I undertake to use the materials and data collected exclusively for the purposes set out in the protocol and to publish the results whether they are favorable or not. I accept the responsibilities for the scientific conduction of the above project.

Data: _____/_____/_____ _____
Signature

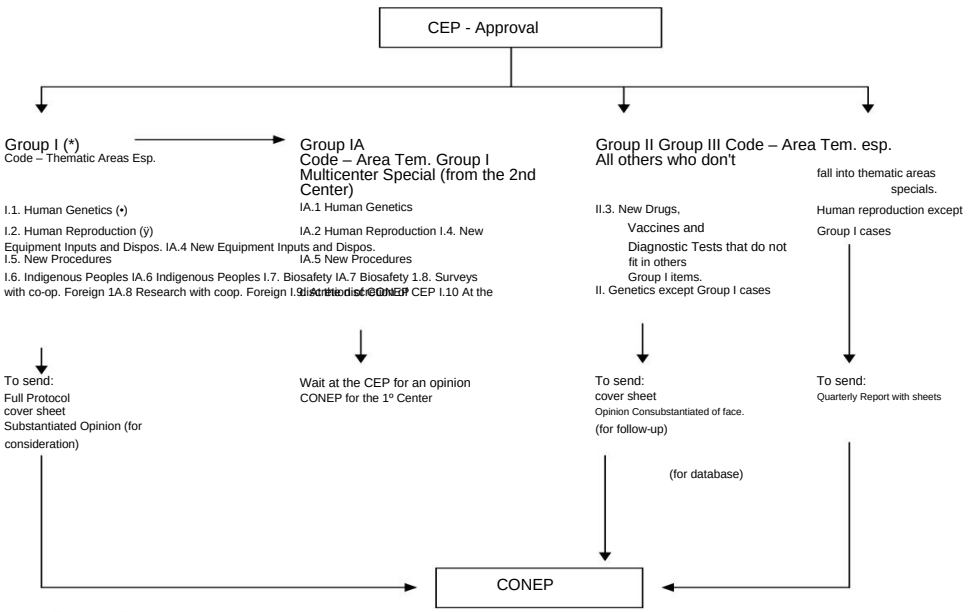
INSTITUIÇÃO ONDE SERÁ REALIZADO			
26. Name:		**29.** Address (Street, no.):	
27. Unit/Organ:		**30.** POCKET:	**31.** City: **32.** U.F.
28. Foreign participation: Yes ( ) No ( )		**33.** Phone :	**34.** Fax.:
35. Multicentric Project: Yes ( ) No ( ) National ( ) International ( )		)	(Attach the list of all Participating Centers in Brazil)

Termo de Compromisso (do responsável pela instituição) : I declare that I know and will comply with the requirements of Res. CNS 196/96 and its Complementary and as this institution has conditions for the development of this project, I authorize its execution

Name:_____ Position _____

Data: _____/_____/_____ _____
Signature

PATROCINADOR			**Não se aplica ( )**
36. Name:		**39.** End of reception	
37. Respons:		**40.** POCKET:	**41.** City: **42.** UF
38. Position / Function:		**43.** Phone :	**44.** Fax:
COMITÊ DE ÉTICA EM PESQUISA - CEP			
45. Entry date: ____/____/____	**46.** Registration in the CEP:	**47.** Conclusion: Approved ( ) Data: ____/____/____	**48.** Not approved ( ) Data: ____/____/____
49. Report(s) of the Responsible Researcher expected to: Data: ____/____/____ Data: ____/____/____			
Forward to CONEP: **50.** The above data for registration ( ) The project for appreciation ( ) **52.** Data: ____/____/____		**53.** Coordinator/Name _____ Signature	**Anexar o parecer consubstanciado**
COMISSÃO NACIONAL DE ÉTICA EM PESQUISA - CONEP			
54. File No : **55.** Process :	**56.** Receiving date :	**57.** Registration with CONEP:	
58. Observações:			



CÓDIGO – ÁREAS DO CONHECIMENTO (Folha de Rosto Campos 2 e 3)

1 – CIÊNCIAS EXATAS E DA TERRA
1.01 – MATEMÁTICA
1.02 – PROBABILIDADE E ESTATÍSTICA
1.03 – CIÊNCIA DA COMPUTAÇÃO
1.04 – ASTRONOMIA
1.05 – FÍSICA
1.06 – QUÍMICA
1.07 – GEOCIÊNCIAS
1.08 – OCEANOGRAFIA

2 – CIÊNCIAS BIOLÓGICAS (*)
2.01 – BIOLOGIA GERAL
2.02 – GENÉTICA
2.03 – BOTÂNICA
2.04 – ZOOLOGIA
2.05 – ECOLOGIA
2.06 – MORFOLOGIA
2.07 – FISIOLOGIA
2.08 – BIOQUÍMICA
2.09 – BIOFÍSICA
2.10 – FARMACOLOGIA
2.11 – IMUNOLOGIA
2.12 – MICROBIOLOGIA
2.13 – PARASITOLOGIA
2.14 – TOXICOLOGIA

3 – ENGENHARIAS
3.01 – ENGENHARIA CIVIL
3.02 – ENGENHARIA DE MINAS
3.03 – ENGENHARIA DE MATERIAIS E METALÚRGICA
3.04 – ENGENHARIA ELÉTRICA
3.05 – ENGENHARIA MECÂNICA
3.06 – ENGENHARIA QUÍMICA
3.07 – ENGENHARIA SANITÁRIA
3.08 – ENGENHARIA DE PRODUÇÃO
3.09 – ENGENHARIA NUCLEAR
3.10 – ENGENHARIA DE TRANSPORTES
3.11 – ENGENHARIA NAVAL E OCEÂNICA
3.12 – ENGENHARIA AEROESPACIAL

4 – CIÊNCIAS DA SAÚDE (*)
4.01 – MEDICINA
4.02 – ODONTOLOGIA
4.03 – FARMÁCIA
4.04 – ENFERMAGEM
4.05 – NUTRIÇÃO
4.06 – SAÚDE COLETIVA
4.07 – FONOAUDIOLOGIA
4.08 – FISIOTERAPIA E TERAPIA OCUPACIONAL
4.09 – EDUCAÇÃO FÍSICA

5 – CIÊNCIAS AGRÁRIAS
5.01 – AGRONOMIA
5.02 – RECURSOS FLORESTAIS E ENGENHARIA FLORESTAL
5.03 – ENGENHARIA AGRÍCOLA
5.04 – ZOOTECNIA
5.05 – MEDICINA VETERINÁRIA
5.06 – RECURSOS PESQUEIROS E ENGENHARIA DE PESCA
5.07 – CIÊNCIA E TECNOLOGIA DE ALIMENTOS

6 – CIÊNCIAS SOCIAIS APLICADAS
6.01 – DIREITO
6.02 – ADMINISTRAÇÃO
6.03 – ECONOMIA
6.04 – ARQUITETURA E URBANISMO
6.05 – PLANEJAMENTO URBANO E REGIONAL
6.06 – DEMOGRAFIA
6.07 – CIÊNCIA DA INFORMAÇÃO
6.08 – MUSEOLOGIA
6.09 – COMUNICAÇÃO
6.10 – SERVIÇO SOCIAL
6.11 – ECONOMIA DOMÉSTICA
6.12 – DESENHO IDUSTRIAL
6.13 – TURISMO

7 - CIÊNC IAS HUMANAS
7.01 – FILOSOFIA
7.02 – SOCIOLOGIA
7.03 – ANTROPOLOGIA
7.04 – ARQUEOLOGIA
7.05 – HISTÓRIA
7.06 – GEOGRAFIA
7.07 – PSICOLOGIA
7.08 – EDUCAÇÃO
7.09 – CIÊNCIA POLÍTICA
7.10 – TEOLOGIA

8 - LINGÜÍSTICA, LETRAS E ARTES
8.01 - LINGÜÍSTICA
8.02 - LETRAS
8.03 - ARTES

(*) NÍVEL : (Folha de Rosto Campo 4)

(P) Prevenção
(D) Diagnóstico
(T) Terapêutico
(E) Epidemiológico
(N) Não se aplica

(*) NOTE: Research in thematic areas 3 and 4 (new drugs and new equipment) that depend on an import license from Anvisa/MS, must follow the following flow - Projects in area 3 that fall simultaneously in other areas that depend on Conep's approval, and those from area 4 must be sent to Conep, which will send them to Anvisa/MS with its opinion. – Exclusive projects in area 3, approved by the CEP (Res. CNS No. 251/97 – item V.2), must be sent to Anvisa by the sponsor or researcher.

Annex C - Checklist

National Research Ethics Commission

Documents for Research Project Analysis – Prot. zip code no. _____

Reg. Conep n.º _____

Classification in the Flowchart:
Group I ( ) Special Thematic Area _____
Group II ( )
Group III ( )

Note: Items marked with ÿ correspond to mandatory documents without which the protocol cannot be accepted at the CEP for analysis. Check upon delivery of the protocol.

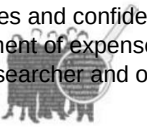
The other items will be evaluated by the rapporteur.

	Yes	No	
ÿ			Title page – FR (October/99 version)
ÿ			Portuguese research project
			Background and justification, registration in the country of origin, in the case of drugs and health devices
			Description of material and methods, casuistry, expected results and bibliography
			Critical analysis of risks and benefits
			Duration (execution schedule)
			Responsibilities of the researcher, the institution, the sponsor
			Criteria for suspending or terminating
			Place of realization of the various stages
			Necessary infrastructure and agreement of the institution (F)
ÿ			Detailed financial budget and researcher remuneration
			Ownership of information
			Population characteristics (FR field 10), justification for use by vulnerable groups
			Number of subjects locally and globally (multicentric - FR field 9)
			Description of methods that affect research subjects
			Material sources, specific collection
			Recruitment plans, inclusion and exclusion criteria
ÿ			Free and informed consent form
			How and who will get it
			Description of risks with severity assessment
			Risk protection measures and confidentiality
			Forecast of reimbursement of expenses
ÿ			Resume of the main researcher and other researchers

FREE AND INFORMED CONSENT (content)

Yes	No	
		accessible language
		Justification, objectives and procedures
		Discomforts and risks
		Expected benefits
		Existing Alternative Methods
		Form of assistance and responsible name and telephone number of the researcher and zip code

omo and who r oo
Description of risks with severity assessment
Risk protection measures and confidentiality
Forecast of reimbursement of expenses
ÿ Resume of the main researcher and other researchers



FREE AND INFORMED CONSENT (content)

Yes	No	
		accessible language
		Justification, objectives and procedures
		Discomforts and risks
		Expected benefits
		Existing Alternative Methods
		Form of assistance and person in charge (researcher's name and telephone number and CEP)
		Clarifications before and during the research on the methodology
		Possibility of inclusion in a control or placebo group
		Freedom to refuse or withdraw consent without penalty
		Confidentiality and privacy guarantee
		forms of reimbursement
		Compensation forms

RESEARCH CONDUCTED FROM ABROAD OR WITH FOREIGN COOPERATION

Yes	No	
		Commitments and advantages for research subjects
		Commitments and benefits for the country
		Identification of the researcher and national institution co-responsible (Schedule of Face)
		Document of approval by the Ethics Committee in the country of origin or yes no justification
		Responding to the need for personnel training in Brazil
		Lists of participating centers abroad and in Brazil

RESEARCH CONDUCTED FROM ABROAD OR WITH FOREIGN COOPERATION

RESEARCH WITH NEW DRUGS, VACCINES AND DIAGNOSTIC TESTS

Yes	No	
		Current phase and demonstration of compliance with previous phases
		Pharmacological substance – registration in the country of origin and status of research.
		Pre-clinical information – researcher's brochure (BPPFC**)
		Clinical information from previous phases
		Justification for the use of placebo or wash out
		Access to the drug, if its superiority is proven Statement by the
		researcher that he/she agrees and will follow it (Cover Sheet)
		Justification of inclusion of healthy subjects
		Forms of recruitment

RESEARCH IN INDIGENOUS PEOPLES

yes	no	
		Commitment to obtain the consent of the communities involved, for through the respective indigenous organizations or local councils (without prejudice to individual consent) that will designate the intermediary for contact between the researcher and the community.
		Description of the process for obtaining and registering the Free and Informed Consent Form - TCLE

To send the protocol to Conep for consideration (Group I Research), add:

Yes	No	
		Institutional CEP referral letter
		Document of approval by the CEP, with substantiated opinion

Annex D – Guidelines for the researcher to be attached to the Substantiated Opinion of the CEP

A - (To report Approved or Approved with Recommendations)

- The research subject is free to refuse to participate or to withdraw his consent at any stage of the research, without any penalty and without prejudice to his care (Res. CNS No. 196/96 – Item IV.1 .f) and must receive a copy of the Free and Informed Consent Term, in full, signed by him (Item IV.2.d).
- The researcher must develop the research as outlined in the approved protocol and discontinue the study only after analyzing the reasons for discontinuation by the CEP that approved it (Res. CNS Item III.3.z), awaiting its opinion, except when perceiving risk or harm not foreseen to the participating subject or when the superiority of the regimen offered to one of the research groups (Item V.3) that requires immediate action is verified.
- The CEP must be informed of all adverse effects or material facts that alter the normal course of the study (Res. CNS Item V.4). It is the researcher's role to ensure adequate immediate measures in the event of a serious adverse event that has occurred (even if it has been in another center) and to send a notification to the CEP and the National Health Surveillance Agency (Anvisa), along with their position.
- Any modifications or amendments to the protocol must be presented to the CEP in a clear and succinct manner, identifying the part of the protocol to be modified and its justifications. In case of Group I or II projects previously submitted to Anvisa, the researcher or sponsor must also send them to Anvisa, together with the CEP's approval report, to be added to the initial protocol (Res. n.º 251/97, item III.2.e).
- Partial and final reports must be submitted to the CEP, initially on ____/____/____ and at the end of the study.

B - For projects in Group 1 of the flowchart, add:

Your project (Registration _____ Group _____ Special thematic area) is being forwarded to Conep and can only be started after approval by the latter.

C - (To appear Pending)

Complementary information to the researcher, to be attached to the opinion of the CEP.

- The researcher has 60 days to respond to the questions formulated by the CEP in its opinion. After this period, the project will be considered withdrawn and later, if there is interest, a new protocol must be presented and the registration process restarted (Res. CNS No. 196/96).
- Any modifications or amendments to the protocol must be presented to the CEP in a clear and succinct manner, identifying the part of the protocol to be modified and its justifications.

Annex E - Terminology for research project interruptions

Project withdrawn – when, after 60 days of receiving a pending opinion from the CEP or Conep, the researcher does not express an opinion on the questions presented.

Protocol canceled – when the interruption occurs before the start of the recruitment of research subjects or effective data collection.

Suspended protocol – when the interruption occurs during research in progress.

Protocol closed – when it is finalized after the foreseen steps have been completed.

Annex F - CEP registration and update form

MINISTRY OF HEALTH

NATIONAL COMMISSION ON RESEARCH ETHICS - CONEP

RESEARCH ETHICS COMMITTEE - CEP

CEP REGISTRATION FORM

Initial registration ( ) Renovation ( ) Data change ( )

Institution:

Complete address:

City: **UF:** POCKET:

CNPJ:

phone:( ) **Fax: (**) ***E-mail:***

President / Director:

Legal nature: **PRIVATE (**) **PUBLIC (**)

CONSTITUTION OF THE ETHICS COMMITTEE

Total members:

Data: ____/____/_____

Name	Sex	Profession/Specialty	Highest Degree
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			
10.			

User Representative:

Address: POCKET: **Such.**

Indicated by which Entity/Association:

Address: POCKET: **Such.**

Coordinator:

full address of

Committee:

City: POCKET:

Fone: ( ) ( ) **Fax: (**)

E-mail:

Administrative employee

1. Attach the act of creation of the CEP (by the institution's management), summary description of the institution, criteria for choice of members and appointment of the user representative. According to Res. 196/96, item VII.9, after three years the CEP renewal must be requested through this form model Any changes in the composition of the CEP must be informed immediately in this same model.

SCRIPT OF CONsubstantiated OPINION

To substantiate – link, unite, unify, consolidate – the opinion of the CEP or Conep on the research project is the result of the confrontation, mixture and convergence of opinions in the collegiate. As an official communication tool to the researcher about the evaluation of his project, it must have the following characteristics:

- clarity
- objectivity
- conciseness
- completeness
- reasoning
- directivity
- compliance with standards

Thus, the opinion must necessarily inform:

- Data identifying the research project (name of the project, responsible researcher, responsible institution, CEP of origin, thematic area);
- Brief description of the project's justifications and objectives;
- Clear description of the project design and methodologies (experimental groups, procedures, outcome indicators, type of study, research phase);
- Brief reference to the criteria for participation (recruitment, criteria for inclusion/exclusion, research interruption);
- Identification of risks and possible benefits to subjects.

Based on the aspects reported, the opinion should always consider:

- Relevance and scientific value of the proposed study;
- Adaptation of the methodology to the objectives pursued;
- Degree of vulnerability of the subjects and proposed protective measures;
- Assessment of the risk-benefit binomial.

Still in the considerations, the opinion must always explain the observation of compliance with the requirements of the CNS Resolutions regarding research with human beings, in particular:

- Complete and adequate instruction of the process;
- Presence of the required commitments from the responsible researcher, sponsor and institution;

- Identification of those responsible for attendance, monitoring and receiving of the referred subjects, when applicable.
- Guarantee of the research subject's fundamental rights (information, privacy, innocuous refusal, withdrawal, indemnification, reimbursement, continuity of care, access to the researcher and CEP, etc.);
- Proper treatment of biological data and materials;
- Consistency and acceptability of justifications for the presence of alert circumstances (use of placebo, washout, non-participation of the country of origin or lack of approval by the ethics committee in this country, etc).

The Consent Form will deserve special consideration, with the critical observation of the following characteristics:

• Conciseness and objectivity;
• Language appropriate to the sociocultural level of the research subjects; • Sufficient description of procedures; • Identification of expected risks and discomforts; • Explanation of the aforementioned guarantees.

Common vices in the Consent Terms must be rejected:

• Exaggeration of benefit expectations; •
Minimization of risks and discomforts; •
Restrictive assertions of the subjects' rights; •
Authorization for unjustified opening of data and medical records; •
Authorization for indefinite and/or unjustified storage of material biological.

The conclusion of the opinion must be clear and objective, in the following terms:

• Indication of one of the expected results (approval, pending, non-approval); • Enumeration of pending issues or reasons for non-approval.

The substantiated opinion should always avoid:

• Observations of a personal nature; •
Unsubstantiated claims or innuendo; • Laconic expressions and formatting as a form.

The opinion must be signed by the coordinator of the CEP or Conep, citing the date of the meeting that produced it. The referral to Conep must always be referred to and communicated to the researcher, with the alert waiting for his/her pronouncement before the beginning of the study.

The report of rapporteurs to the committee should follow the same structure.

Annex G - Guidance on instruction of the protocol of research for ethical evaluation

Conep has been putting on hold several projects that are sent to it incompletely or with some clauses that violate or contradict the provisions of the CNS regarding ethics in research on human beings.

Instead of filing or returning the protocols, Conep purposely preferred to keep them pending, as a way of improving the evaluation system.

In early 2004, Conep warned that the protocols presented without the proper data would be archived. This system, in order not to cause major problems for the new CEPs, was taken gradually.

In 2005, Conep considers this phase to be over and, therefore, from April onwards, the protocols that do not contemplate the provisions of Resolutions n.º 196/96, 251/97, 292/99, 303/00, 340/04, 346/05 and 347/05 or that contain a clause that contradicts the provisions of the aforementioned resolutions, will be returned to the CEPS, with the stamp of “Archived”.

Obviously, at any time, the protocol, duly instructed, can be resubmitted, receiving a new number, as a “new project”.

Projects in which there are doubts or questions of a conceptual and/or doctrinal nature will remain pending.
That said, Conep asks researchers (via CEP) and CEP to pay special attention to ensuring that the protocols are properly instructed in accordance with the CNS Resolutions.

Due to their importance and in order to facilitate the work of the CEP, some of the reasons for “pending” due to incomplete or inadequate instruction in the protocol are listed below, and it is suggested that they be used as a basic checklist.

Issues whose absence often leads to pendency such as incomplete and/or inadequate instruction

In the foreign cooperation protocols (Res.CNS no. 196/96 and 292/99)

• Identification of the international coordinator/author/principal researcher of the project. • Identification of the country of origin. Data to be clarified in the protocols, as they constitute criteria for characterizing the country of origin: country where the research is designed and/or where the main researcher, author or international coordinator works; country where the product to be tested comes from or where the sponsor is based; country to which the data will be forwarded. • Clear information regarding the link between the coordinator/author/principal researcher and the sponsor, with a view to analyzing any possible conflict of interest.
• Justification when the project is not carried out in the country of origin.
• Document of project approval by the Ethics Committee of the country of origin.

If the document is not yet available, inform the date of submission to the committee (and identify the committee).
- Justification for carrying out the subsidiary exams outside Brazil. Information on measures planned for the transfer of technology that does not yet exist in the country.

- List of centers in Brazil and abroad with the total number of subjects and the number in each center. Information on the centers in the country of origin (either the sponsor or the coordinator) where the project will be conducted.
- Description of the research subject's recruitment plans (in which institution they are enrolled, whether they are served by the SUS or by the private system).
- Procedures to guarantee confidentiality and privacy (especially in access to medical records) in line with Brazilian legislation.
- Proposal for continuity of treatment after the end of the study.

In projects with new drugs, medicines, vaccines and diagnostic tests (Res. CNS n.º 196/96 and 251/97)

- Identification (in the title) of the research phase;
- Description of the previous phases, including:

Place where they were performed

Material and method (indicating the number of subjects in each group)
Results

Indication of the publication journal.

- Description of the pre-clinical phase, including:

Place of performance

Material and method (which tests and which animals were used)

Toxicity and other tests (Chapter IV, Res. No. 251/97)
- Indication of conventional treatment already established in the literature for the situation tion on canvas;
- When the use of placebo is foreseen.

Comparative placebo results, in previous phases:

Ethical justification for the use of placebo in the proposed phase

Predictable risks and disadvantages for patients in the placebo group

Literature data already observed with placebo in the situation in question.
- Washout justification;
- Analysis of risks and disadvantages of washout for the research subject;
- In the inclusion criteria:
- Explicit inclusion of subjects already undergoing treatment, with a favorable therapeutic response or not. If so, explain the risks arising from the "washout" or the use of placebo, in each of the situations above.

In projects where material storage is planned, strictly observe Resolution No. 347/05

GENERAL INFORMATION

• It should be noted that the provisions of the resolutions referring to specific thematic areas must be complied with; • In the case of medical research, it is important that the researcher and the CEP manifest themselves regarding the execution of the project in view of the provisions of art. 129 of the Code of Medical Ethics;

• The TCLE must be written by the researcher, in accessible language and cannot contain any restrictive clause on the subject's rights or contradict the provisions of the CNS Resolutions;
• The CEP must forward a substantiated opinion and not a checklist with X;

• Answers to pending issues must be prepared by the researcher and, after evaluation by the CEP, sent to Conep;
• Conep's relationship is direct with the researcher, the institution and the CEP;
• The CEP must send the list of evaluated projects on a quarterly basis. Those with Sisnep implemented do not need to send the Cover Sheets, being able to use Sisnep's own tables; • The user representative must be appointed in accordance with Resolution No. 240/97 and must, as a member of the CEP, participate as a protocol reporter;

• The CEP must be up to date with the registration, that is, it must be renewed with Conep every three years.

Glossary

Chance (statistics): 1. term used to describe the results of a stochastic process, that is, a process in which the probability of any event occurring is known or can be determined. 2. it is said of the result of the sum of a complex of numerous causes whose individual actions we do not know. 3. by chance: it does not mean, in statistics, haphazardly, without reflection, inadvertently, but the opposite: it means a process constructed so that each possible outcome is associated with a known probability.

Chance (general): 1. uncertain or unpredictable event; chance, eventuality. 2. fortuitous. 3. fate, fortune, luck. 4. at random: haphazardly, without reflection, inadvertently.

Adherence to treatment: degree to which a patient follows the treatment that has been assigned to him.

Random: (statistics) 1. that it happens by chance, that is, it is said of the variable that assumes values according to a certain law of probability. For example, the results of a dice game are random. 2. when it is determined by a complex of numerous causes added together, but whose individual performances we do not know. For example, random error. 3. it is said of the process constructed so that each possible outcome is associated with a known probability. For example, in one experiment, treatments are assigned to patients by random process.

Allocation: process of allocating or assigning a treatment to an experimental unit.

Sample: any set whose characteristics or properties are studied with the aim of extending them to another set, of which the first set is considered a part.

Data collection: process of taking raw data, recorded in clinical records or laboratory notebooks, and organizing them in a satisfactory way for later tabulation and analysis.

Database collection or archive of data organized in a specific way and only accessed by personnel with the necessary competence, for a defined purpose.

Centralized database: especially in multicenter studies, database kept in one place.

Blocks: in statistics, sets of experimental units as similar as possible, formed, for example, by subgroups of patients classified according to one or more variables, almost always baselines. Treatments are randomly allocated within blocks. See also strata.

Trial arm: term used in place of treatment or group. It should be avoided.

Sample size calculation: mathematical calculation, usually done when the trial is planned, that establishes the number of patients that should be recruited at a given level of significance and a given test power.

Casual: Same as random.

Randomization: procedure adopted in randomized clinical trials; it consists of assigning, by random process, pre-chosen treatments to the patients participating in the research. See randomization.

Casuistry: detailed record of clinical cases of the diseases.

Clinical center: in the context of clinical trials, it is the organizational structure responsible for recruiting, registering and treating patients, to generate the data required in the clinical trial.

Center: in the context of clinical trials, each unit is autonomous. The center collects, sorts, evaluates, analyzes data or provides logistical support to the trial. Includes clinical center, data analysis center, central laboratory, offices, libraries, quality control center.

Treatment Comparison: Any comparison involving two or more treatments or groups.

Multiple comparisons: refers to the fact that two or more treatments must be compared, always in relation to the same variable, at a given moment of the trial (usually at the end).

Suspension Condition: A condition encountered while performing a certain procedure (for example, when examining a patient) that requires the person performing the procedure to suspend the process until the condition is removed.

Termination Condition: A condition encountered when performing a certain procedure (eg, when examining a patient) that requires the person performing the procedure to stop the process.

Confounding: Confounding is said to exist when the effect of the treatment is confounded with the effect of other factors, in such a way that the effect of the treatment alone cannot be determined. Thus, confounding between sex and drug could mean, for example, that the drug was only administered to men and a placebo was administered to women.

Historical control: group of patients with the same disease or condition as the experimental group, but diagnosed and treated in the conventional way in a period of time prior to the period in which the patients in the experimental group were diagnosed and treated.

Negative control: treatment without any pharmacological or physiological effect, that is, placebo or pseudoprocedure. See positive control.

Positive Control: Usually the standard treatment, but always a treatment that involves the use of a pharmacologically active substance. See negative control.

Simultaneous control: group of patients with the same disease or condition as the experimental group, submitted to the control treatment in exactly the same period of time as the patients in the experimental group. See also historical control.

Data: effective information in the form of measurements, observations or statistics, used as a basis for argumentation.

Raw data: measurements and observations recorded in clinical records or laboratory notebooks, but not yet organized for interpretation. 2. Lists of data obtained by computer, but in the form in which they were collected, before editing, summarization and analysis.

Design: the part of the test that specifies the procedures that will be evaluated, the experimental units, the variable under analysis and the way in which procedures will be assigned to the experimental units. See also drawing.

Fixed-Size Sample Design: Design in which the number of research participants is fixed before the start, either through sample size calculation or other considerations (eg, what is usual in the area, availability). It is conventional to establish the initial sample size, unless the study is a sequential analysis. See sequential analysis.

Design: the same as design. It is used because it sounds similar to *design,* the English term that translates. However, the term design is more appropriate.

Discrepant *(outlier):* value, reading or measurement outside the established limits and, therefore, questioned or considered an error.

Medical device: device for diagnosis or therapy that does not chemically interact with the person's body. It includes diagnostic tests, equipment, pacemakers, *kits,* intraocular lenses, orthopedic devices.

Random **distribution of treatments:** The process of assigning treatments to patients at random using, for example, a table of random numbers. This procedure is only adopted in randomized clinical trials. See random distribution of treatments.

Distribution of treatments by blocks: the same as distribution of treatments by strata.

Distribution of treatments by strata: treatment distribution scheme in which patients are first classified into subgroups, strata or blocks, according to one or more baseline variables. The treatments are then randomly assigned within the blocks.

Treatment distribution according to best: treatment distribution scheme in which the treatment assigned to a patient is a function of the success or failure of the treatment given to the previous patient. For example, a success of the test treatment dictates that the next patient undergoes that treatment. A failure determines that the next patient is a control. The idea is to minimize the number of patients assigned to the inferior treatment.

Random distribution of treatments: the same as random distribution of treatments.

Uniform treatment distribution: A treatment distribution scheme in which all patients are equally likely to receive any one of the treatments under test.

Data Editing: The process of reviewing data in order to detect deficiencies or errors in the way it was recorded or collected.

Treatment effect: in clinical trials, the difference between the results observed in the experimental group and in the placebo control group.

Placebo effect: effect produced by placebo.

Endpoint: primary or secondary event that, if observed in the patient, leads to the termination or change of treatment or follow-up.

Trial: Any experimental action taken for the purpose of obtaining data for judgment or conclusion. Same as experience.

Clinical trial: research activity that involves the administration of a test treatment (eg, a drug, a surgical procedure, or a medical device) to an experimental unit for the purpose of evaluating the treatment. In most cases, the experimental unit is man, but it can be an experimental animal. See experimental unit.

Randomized *Clinical Trial (RCT)* – see randomized controlled trial.

Comparative clinical trial: a clinical trial that involves the comparison of two or more treatments. See controlled clinical trial.

Randomized controlled clinical trial - *Randomized Clinical Trial* (RCCT): clinical trial that involves at least one test treatment and one control treatment, with simultaneous recruitment and follow-up of all groups, and where treatments are assigned to patients on a random basis, in such a way that neither patients nor guardians by the selection and treatment of these patients can influence the allocation of treatments and where the allocations remain unknown to patients and clinical staff until the end. Allocation is known to patients and clinicians only by codes, preferably numerical.

Controlled clinical trial: a clinical trial that involves one or more test treatments and at least one control treatment.

Placebo-Controlled Clinical Trial: A clinical trial in which patients assigned to the control group receive placebo.

Equivalence trial: randomized controlled clinical trial whose purpose is not to test the hypothesis of equality, but the hypothesis of equivalence, that is, that the difference between treatments is not greater than the “equivalence value” , a difference considered unimportant from the clinician's point of view.

Equivalence assay with positive control *(Active Control Equivalence* – ACE): equivalence trial in which a control group subjected to placebo is not used, but only a positive control.

Rotational assay: assay involving rotational treatments.

Data entry: process of keying in data for electronic storage.

Type I error : it consists of rejecting the null hypothesis when it is true.

Type II error: it consists of accepting the null hypothesis when it is false.

Test statistics: formula or algorithm used for a significance test; the numerical value calculated by this formula or this algorithm, for a specific test of significance, using a data set.

Stratification: process of classifying experimental units into strata, for further randomization or analysis.

Strata: in statistics, the same as blocks. The term block comes from the agricultural area and the term stratum from the social area.

Study: a generic term used to indicate a wide variety of research activities that involve data collection, analysis and interpretation. Also used as a synonym for clinical trial.

Comparative study: study that involves two or more groups of patients to compare and judge the influence of some factor, condition, characteristic, or procedure, present or applied to one of the groups, but not to the other. Synonymous with clinical trial if the study requires the comparison of different treatments involving patients treated in the same period of time.

Cohort study: study that involves the identification of a large number of people (cohort), some exposed to a suspected causal factor, others not exposed to that factor. These people are followed over a relatively long period of time to verify whether or not an outcome or condition of interest has occurred. Then, the proportions of occurrences in the two groups are compared, that is, in people exposed to the suspected causal factor and in those not exposed. Also called prospective study.

Case-Control Study: A study that involves identifying people with a disease or condition of interest (cases) and a comparable group of people without the disease or condition of interest (controls). Cases and controls are compared with respect to some existing, past, or exposure attribute believed to be related to the disease or condition. Also called a retrospective study.

Pilot Study: Preliminary study designed to indicate whether a larger study is feasible. Also used to establish the sample size.

Prospective study: study in which people with a specific characteristic or attribute are identified and observed over a period of time to verify whether or not an outcome or condition of interest has occurred.

Retrospective Study: A study in which people with a characteristic or disease are identified and asked whether or not they have been exposed to a particular factor.

Secondary or ancillary study: a study stimulated by the trial and conducted with the aim of generating information of interest to the trial, designed and conducted by researchers from one or more centers participating in the trial, using resources from the trial itself (e.g., money, patients, staff, etc.).

Serious adverse event EAS: A serious adverse event is any untoward medical occurrence that results in: death, life-threatening or life-threatening, hospitalization or prolongation of a pre-existing hospitalization other than elective surgeries and hospitalizations provided for in the protocol, persistent disability or significant, congenital anomaly or birth defect, and significant medical occurrence.

Experiment: scientific work that aims to verify a physical phenomenon; rehearsal, attempt.

Blind trial: procedure adopted only in clinical trials, which consists of keeping all clinical staff, especially those responsible for treating and evaluating patients, not knowing what treatments were administered to patients. In this way, the expectation of researchers about the result of the research does not influence the results of the exams. See masked experiment.

Double- **masked experiment:** the same as double blind.
Double-blind or double-blind experiment: procedure adopted only in clinical trials that consists of keeping all clinical personnel, especially those responsible for treating and evaluating patients, and the patients themselves, unaware of the treatments administered; treatments are identified by means of codes, preferably numerical. See doubly masked experiment.

Masked experiment: Same as blind experiment. Some English-speaking researchers have recommended using the term masked rather than blind to avoid potential confusion, particularly when used in experiments where the measure of interest is vision loss, or in experiments involving patients who have lost sight. .

Multicenter experiments: experiments conducted in two or more centers, always with a common protocol, but with a central administration and a single center to receive and process the data.

Phase I: first phase of testing a new drug in man. The studies are designed to generate preliminary information about the chemical action and safety of the drug. Normally, healthy volunteers are used. Often it is not done with another group.

Phase II: second phase of testing a new drug in man. The studies are done in patients with the disease or those with the condition of interest, to test the efficacy and prove the safety of the drug. Usually, but not always, a placebo control.

Phase III: third, and usually final, phase of testing a new drug in man. It must prove the effectiveness of the new drug in relation to others. Trials typically include control (negative, positive, or both) and randomization of patients to groups.

Phase IV: trials designed to assess the long-term safety of the drug's use and its effectiveness for unstudied populations, such as children and the elderly.

Risk factor: environmental exposure, personal characteristic or event that affects the probability of contracting a certain disease or experiencing a change in health status. A risk factor analysis usually involves some sort of statistical analysis to pinpoint or identify risk factors for a particular disease or condition.

FDA – *Food and Drug Administration:* Drug and Food Products Administration, an American federal agency located in Rockville, Maryland, which has, among other attributions, to legislate on clinical research conducted in the United States with federal funds.

Follow-up: follow-up of the patient.

Control group: in a clinical trial, a group of patients assigned to the control treatment. It serves as a basis of comparison for the group receiving the test treatment.

Experimental group: In a clinical trial, this is the group of patients assigned to the test treatment. It is contrasted with the control group to reach a conclusion about a factor, condition, or treatment.
Treated group: the same as the experimental group.

Alternative hypothesis: alternative to the null hypothesis, which postulates that there is a difference between the populations or groups in comparison, with respect to the factor, characteristic or condition of interest. See null hypothesis.

Nullity hypothesis: hypothesis that postulates that there is no difference between the populations or groups in comparison, with respect to the factor, characteristic or condition of interest. See null hypothesis.

Null hypothesis: current but mistaken translation of *null hypothesis,* since it is not the hypothesis that has the quality of null, but what it postulates (null difference). See null hypothesis.

Natural history of a disease: course of a disease that has gone untreated.
A study of the natural history of a disease or condition would therefore yield information about the course of a disease or condition that has gone untreated.
In clinical trials, it is the information produced by the control group when the control treatment is a placebo.

IDE – *Investigational Device Exemption:* acronym used by the FDA to designate a medical device that is being evaluated in humans, either by the manufacturer or by an independent researcher (see IND as the corresponding term for drugs).

IND – *Investigational New Drug:* acronym used by the FDA to designate a new drug under study (see IDE as a corresponding term for medical devices).

Patient enrollment: the act of enrolling or enrolling a patient in a clinical trial. The process of enrolling or enrolling a patient in a clinical trial includes all examinations and data collection procedures to establish whether the patient is eligible.

Interaction: situation in which the magnitude of the difference of two treatments or groups – for example, experimental and control group – depends on the value taken by a third factor unrelated to the treatment (for example, there is an interaction between sex *versus* treatment if the difference between experimental and control group has one value for men and another, statistically different, for women).

Baseline: point in time or dataset that serves as a basis for measuring changes in the variables of interest.
MEDLARS – ***Medical Literature Analysis Retrieval System: Medical Literature Analysis Retrieval System .***

MEDLINE – Online Medical Literature Analysis Retrieval System : ***Online Medical Literature Analysis Retrieval System .***
Performance monitoring: ongoing process, throughout a clinical trial, to assess the performance of a site or group of sites.

Non-random: any method that does not conform to the statistical definition of chance; term used by statisticians to emphasize the nature of a random or systematic process. See also non-casual.

Non-random: the same as non-random.

NIH – ***National Institutes of Health:*** United States Institutes of Health.

Significance level: probability of committing a type I error, in a hypothesis test, with a specified statistic.

Nocebo: harmless substance whose action theoretically should not produce any reaction but, when associated with psychological factors, ends up producing a harmful effect in some individuals.

Random or random number: number generated by a defined random process.

Patient: in the research context, the term always refers to the patient who participates, or has been invited to participate, in the research.

Parameter: in statistics, it is the constant that, in a mathematical expression, characterizes a population or a process; its value is generally unknown, but can be estimated. 2. in clinical medicine, it is the variable whose measurement is indicative of a quantity or function that cannot be determined by direct methods. For example, blood pressure and pulse rate are parameters of cardiovascular function.

Participant: the same as subject, that is, it can be a patient or just a volunteer who participates in a study.

Placebo: a pharmacologically inactive agent given to a patient as a substitute for an active agent to ensure that the patient's response is explained by the drug rather than the fact that it is supposed to be treated.

Test power: probability of rejecting the null hypothesis when it is false.

Cut point: point, in an ordered succession of values, that separates these values into two parts.

Population: all patients who could eventually be recruited for a study.

Stochastic process: it is said of the process that depends on or results from a random variable.

Pseudoprocedure: procedure similar to the real one, performed on a patient with the purpose of the patient (and, sometimes, the doctor) not knowing if the procedure adopted, for that patient, was the real one.

p-value: value associated with a test statistic that indicates the probability of a value as extreme, or more extreme than the observed, occurring only by chance in several repetitions of an experiment.

Randomized or randomized: random.

Randomization: See randomization.

Placebo reactor: patient who is receiving a placebo, does not know this and reports having side effects normally associated with the test treatment.

Patient recruitment: process of identifying patients who can enroll in a clinical trial.

Record: paper or electronic document that contains, or is designed to contain, a set of facts relating to an occurrence.

Statistical significance: it is said that there was statistical significance when the null hypothesis was rejected by a statistical test.

Subgroup: part of the study population, distinguished from the rest by a particular characteristic or a set of characteristics (for example, men under 45 years of age).

Study subject: generic term that designates an individual who participates in a study. The advantage of the term, in relation to the term patient, is the fact that it avoids the connotation of disease – useful in cases in which healthy people are studied – and the opposition to an object. See participant.

Life table: a set of data, in tables or graphs, that summarizes the survival (or mortality) of patients, according to some specification, such as age (in most life tables compiled by demographers), or in some other event such as time of disease diagnosis, or time of study, in the case of a clinical trial.

Sample size: 1. number of experimental units in the trial, usually determined by a calculation, but which can also be obtained from some other criterion, for example, studying what is usual in the area or recruiting available units. 2. number of patients involved in a study or number of patients expected to be involved in a study.

Block Size: Number of units that make up a block.

Trend (statistics): 1. Consistent, persistent difference of the statistic in relation to the parameter to be estimated. Also called bias or vice, translates the English word “bias”. 2. evolution of the variable in a certain sense and direction, generally as a function of time. Translates the English word *trend.*

Bias (general): bias, bias, preconceived personal preference that influences the way in which a measurement, analysis, evaluation or procedure is performed or reported.

Significance test: the same as statistical test.

Statistical test: a statistical test is said to have been performed when observed data and a test statistic are used to make a decision to reject a hypothesis or not, and a p-value is associated with this decision. See significance test.

Treatment: in statistics, regimen, method, or procedure tested in a clinical trial or experiment.

Allocated treatment: treatment administered to a patient as indicated at the time that patient decided to participate in the experiment.

Control treatment: A drug, device, or procedure administered in a clinical trial to serve as the standard against which test treatments are evaluated. The control treatment can be a placebo, a pseudoprocedure, a standard treatment, or no treatment, depending on the study design.

Standard treatment: a widely accepted way of treating a particular disease or condition.

Rotational treatments *(crossover):* In clinical trials, two or more treatments are said to be rotational when they are assigned to some patients in one sequence and for other patients in another sequence.

Unit: smallest unit in which the treatment is applied and whose response is not affected by the other units. Basic unit for data collection and analysis.
Typically a patient in human experimentation, but may also be material, or part, of that patient (a blood sample, a tooth) or a collection of individuals in other contexts (e.g., residents of a household, a hospital ward).). Synonymous with experimental unit in experimentation or clinical trials and observational unit in observational studies.

Experimental unit: see unit

Observational unit: see unit

Variable: condition or characteristic observed in each patient (e.g. age, history of myocardial infarction, blood glucose level), which can assume different values and is observed and recorded one or more times throughout the research.

Random variable: variable that can take on any one of a set of different values, each associated with a certain probability.

Binary variable: variable that only assumes one of two possible values, zero or one. See dichotomous variable.

Continuous variable: variable that takes on any value within a specified range.

Dichotomous variable: the same as binary variable.

Discrete variable: variable that only takes on certain values in an interval.
See also continuous variable.

Washout: Temporary suspension of medication to remove the residual effects of the drug in use by the patient.

standards for research involving human beings

(CNS/MS Resolutions)

Resolution No. 196

NATIONAL HEALTH COUNCIL

Resolution No. 196, of October 10, 1996

The Plenary of the National Health Council at its Fifty-ninth Ordinary Meeting, held on October 9 and 10, 1996, in the exercise of its regimental powers and attributions conferred by Law No. 8080, of September 19, 1990, and by Law No. 8,142, of December 28, 1990, Resolves:

Approve the following research regulatory guidelines and standards involving humans:

Preamble

This Resolution is based on the main international documents that issued declarations and guidelines on research involving human beings: the Nuremberg Code (1947), the Declaration of the Rights of Man (1948), the Declaration of Helsinki (1964 and its versions). 1975, 1983 and 1989), the International Agreement on Civil and Political Rights (UN, 1966, approved by the Brazilian National Congress in 1992), the Proposals for International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS/WHO 1982 and 1993) and the International Guidelines for Reviewing the Ethics of Epidemiological Studies (CIOMS, 1991). Complies with the provisions of the 1988 Constitution of the Federative Republic of Brazil and related Brazilian legislation: Consumer Rights Code, Civil Code and Penal Code, Child and Adolescent Statute, Organic Health Law 8080, of 9/19/90 (provides for the conditions of health care, the organization and functioning of the corresponding services), Law No. 8,142, of 12/28/90 (community participation in the management of the Unified Health System), Decree 99,438, of 8/7/90 (organization and attributions of the National Health Council), Decree 98,830, of 1/15/90 (collection of scientific data and materials by foreigners in Brazil), Law 8,489, of 11/18/92, and Decree 879, of 7/22/93 (provide for the removal of tissues, organs and other parts of the human body for humanitarian and scientific purposes), Law No. 8.501, of 11/30/92 (use of corpse), Law No. 8,974, of 1/5/95 (use of genetic engineering techniques and release into the environment of genetically modified organisms), L ei No. 9,279, of 5/14/96 (regulates rights and obligations related to industrial property), and others.

This Resolution incorporates, from the point of view of the individual and collectivities, the four basic references of bioethics: autonomy, non-maleficence, beneficence and justice, among others, and aims to ensure the rights and duties that concern the scientific community, the subjects of research and the state.

The contextual nature of the considerations developed here implies periodic reviews of this Resolution, according to needs in the technoscientific and ethical areas.

It is also noteworthy that each thematic area of investigation and each type of research, in addition to respecting the principles emanating from this text, must comply with sectorial requirements and specific regulations.

II Terms and Definitions

This Resolution adopts the following definitions within its scope:

II.1 Research – class of activities whose objective is to develop or contribute to generalizable knowledge. Generalizable knowledge consists of theories, relationships or principles or the accumulation of information on which they are based, which can be corroborated by accepted scientific methods of observation and inference.

II.2 Research involving human beings – research that, individually or collectively, involves human beings, directly or indirectly, in their entirety or parts of them, including the handling of information or materials.

II.3 Research Protocol – Document covering the description of the research in its fundamental aspects, information related to the research subject, the qualification of the researchers and all responsible bodies.

II.4 Responsible researcher – person responsible for coordinating and carrying out the research and for the integrity and well-being of the research subjects.

II.5 Research institution – organization, public or private, legitimately constituted and authorized in which scientific investigations are carried out.

II.6 Promoter – individual or institution responsible for promoting the search.

II.7 Sponsor – individual or legal entity that financially supports the search.

II.8 Research risk – possibility of damage to the physical, psychic, moral, intellectual, social, cultural or spiritual dimension of the human being, at any stage of a research and resulting from it.

II.9 Damage associated with or resulting from the research – immediate or late harm, to the individual or to the community, with a proven causal link, direct or indirect, resulting from the scientific study.

II.10 Research subject – is the researched participant, individually or collectively, on a voluntary basis, any form of remuneration is prohibited.

II.11 Free and informed consent - consent of the research subject and/or its legal representative, free from vices (simulation, fraud or error), dependence, subordination or intimidation, after a complete and detailed explanation of the nature of the research, its objectives, methods, expected benefits, potential risks and the discomfort it may cause, formulated in a consent form, authorizing your voluntary participation in the research.

II.12 Indemnity – material coverage, in reparation for immediate or late damage caused by the research to the human being submitted to it.

II.13 Reimbursement – coverage, on the other hand, exclusively for expenses arising from the subject's participation in the research.

II.14 Research Ethics Committees (CEP) - interdisciplinary and independent collegiate bodies, with "public munus", of consultative, deliberative and educational character, created to defend the interests of research subjects in their integrity and dignity and to contribute to the development of research within ethical standards.

II.15 Vulnerability – refers to the condition of people or groups that, for whatever reasons or reasons, have their capacity for self-determination reduced, especially with regard to free and informed consent.

II.16 Disability – Refers to the possible research subject who does not have the civil capacity to give their free and informed consent, and must be assisted or represented, in accordance with current Brazilian legislation.

III Ethical Aspects of Research Involving Human Beings

Research involving human subjects must meet fundamental ethical and scientific requirements.

III.1 Research ethics implies:

a) free and informed consent of the target individuals and the protection of vulnerable groups and the legally incapable (autonomy). In this sense, research involving human beings should always treat them in their dignity, respect them in their autonomy and defend them in their vulnerability;

b) balance between risks and benefits, both actual and potential, individual or collective (beneficence), committing to maximum benefits and minimum harm and risks;

c) assurance that foreseeable damage will be avoided (not maleficence);

d) social relevance of the research with significant advantages for the research subjects and minimization of the burden for vulnerable subjects, which guarantees equal consideration of the interests involved, not losing the sense of its socio-humanitarian destination (justice and equity).

III.2 Any procedure of any nature involving human beings, whose acceptance is not yet enshrined in the scientific literature, will be considered as research and, therefore, must comply with the guidelines of this Resolution. The referred procedures include, among others, those of an instrumental, environmental, nutritional, educational, sociological, economic, physical, psychological or biological nature, whether pharmacological, clinical or surgical and with a preventive, diagnostic or therapeutic purpose.

III.3 Research in any area of knowledge, involving human beings, must observe the following requirements:

a) be adequate to the scientific principles that justify it and with concrete possibilities to respond to uncertainties;

b) be based on previous experimentation carried out in laboratories, animals or other scientific facts;

c) be carried out only when the knowledge to be obtained cannot be obtained by any other means;

d) always prevailing the probabilities of the expected benefits over the foreseeable risks;

e) obey the appropriate methodology. If there is a need for the random distribution of research subjects into experimental and control groups, ensure that, a priori, it is not possible to establish the advantages of one procedure over another through literature review, observational methods or methods that do not involve human beings ;

f) have fully justified, when applicable, the use of the placebo, in terms of non-maleficence and methodological necessity;

g) rely on the free and informed consent of the subject of the research wanted and/or its legal representative;

h) have the necessary human and material resources that guarantee the well-being of the research subject, and there must also be an adequacy between the researcher's competence and the proposed project;

i) provide for procedures that ensure confidentiality and privacy, image protection and non-stigmatization, ensuring that information is not used to the detriment of individuals and/or communities, including in terms of self-esteem, prestige and /or economic-financial;

j) preferably be developed in individuals with full autonomy. Vulnerable individuals or groups should not be research subjects when the desired information can be obtained through fully autonomous subjects, unless the research can bring direct benefits to the vulnerable. In these cases, the right of individuals or groups that want to participate in the research must be guaranteed, provided that protection is guaranteed for their legally defined vulnerability and incapacity;

l) always respect cultural, social, moral, religious and ethical values, as well as habits and customs, when research involves communities;

m) ensure that community research, whenever possible, will translate into benefits whose effects continue to be felt after completion. The project must analyze the needs of each member of the community and analyze the differences between them, explaining how they will be respected;

n) guarantee the return of the benefits obtained through the researches for the people and communities where they are carried out. When, in the interest of the community, there is a real benefit in encouraging or encouraging changes in customs or behavior, the research protocol should include, whenever possible, provisions to communicate such benefit to people and/or
or communities;

o) communicate the research results to the health authorities, whenever they can contribute to the improvement of the health conditions of the community, preserving, however, the image and ensuring that the research subjects are not stigmatized or lose self-esteem ;

p) assure research subjects of the benefits resulting from the project, whether in terms of social return, access to research procedures, products or agents;

q) ensure that research subjects are provided with conditions for monitoring, treatment or guidance, as the case may be, in screening surveys; demonstrate the preponderance of benefits over risks and costs;

r) ensure that there is no conflict of interest between the researcher and the research subjects or project sponsor;

s) prove, in research conducted abroad or with foreign cooperation, the commitments and advantages, for the subjects of the research and for Brazil, resulting from its accomplishment.
In these cases, the researcher and the national institution co-responsible for the research must be identified. The protocol must comply with the requirements of the Declaration of Helsinki and include an approval document, in the country of origin, among those presented for evaluation by the Research Ethics Committee of the Brazilian institution, which will require compliance with its own ethical standards. Studies sponsored from abroad must also respond to the training needs of personnel in Brazil, so that the country can independently develop similar projects;

t) use the biological material and data obtained in the research exclusively for the purpose provided for in its protocol;

u) take into account, in research carried out on women of childbearing age or on pregnant women, the assessment of risks and benefits and possible interference with fertility, pregnancy, the embryo or fetus, labor, the puerperium , lactation and the newborn;

v) consider that research on pregnant women should be preceded by research on women outside the gestational period, except when pregnancy is the fundamental objective of the research;

x) provide, in multicenter studies, the participation of researchers who will develop the research in the elaboration of the general design of the project; and z) discontinue the study only after analyzing the reasons for the desistance.
continuity by the CEP that approved it.

IV Free and Informed Consent

Respect for human dignity requires that all research be carried out after the free and informed consent of the subjects, individuals or groups who, by themselves and/or by their legal representatives, express their consent to participate in the research.

IV.1 It is required that the clarification of the subjects be done in accessible language and that necessarily include the following aspects:

a) the justification, objectives and procedures that will be used in the research;

b) the possible discomforts and risks and the expected benefits;

c) existing alternative methods;

d) the form of follow-up and assistance, as well as its consequences responsible;

e) the guarantee of clarification, before and during the course of the research, about the methodology, informing the possibility of inclusion in a control or placebo group;
f) the freedom of the subject to refuse to participate or to withdraw his consent, at any stage of the research, without any penalty and without prejudice to his care;
g) the guarantee of secrecy that assures the subjects' privacy regarding the confidential data involved in the research;
h) the forms of reimbursement of expenses arising from participation tion in research; and
i) the forms of indemnification in the face of eventual damages resulting from the research.

IV.2 The free and informed consent form will comply with the following requirements:

a) be prepared by the responsible researcher, expressing the cum fulfillment of each of the above requirements;
b) be approved by the Research Ethics Committee that endorses the investigation;
c) be signed or identified by fingerprint, by each and every one of the research subjects or by their legal representatives; and

d) be prepared in two copies, one being retained by the research subject or his/her legal representative and one filed by the researcher.

IV.3 In cases where there is any restriction on freedom or on the clarification necessary for adequate consent, the following must also be observed:

a) in research involving children and adolescents, people with mental disorders or illness and subjects in a situation of substantial decrease in their consent capacities, there must be a clear justification for the choice of research subjects, specified in the protocol, approved by the Research Ethics Committee , and comply with the requirements of free and informed consent, through the legal representatives of the referred subjects, without suspension of the individual's right to information, within the limit of their capacity;
b) freedom of consent should be particularly guaranteed for those subjects who, although adults and capable, are exposed to specific conditioning or to the influence of authority, especially students, military personnel, employees, prisoners, inmates in rehabilitation centers, homes- shelter, asylums, religious associations and the like, assuring them of complete freedom to participate or not in the research, without any reprisals;

c) in cases in which it is impossible to register free and informed consent, this fact must be duly documented, with an explanation of the reasons for the impossibility, and the opinion of the Research Ethics Committee;

d) research on people diagnosed with brain death can only be carried out provided that the following conditions are met:

- document proving brain death (certificate of death);
- explicit consent of family members and/or legal guardian, or prior expression of the person's will;
- total respect for human dignity without mutilation or violation of the body;
- no additional economic and financial burden to the family;
- without prejudice to other patients awaiting hospitalization or treatment;
- possibility of obtaining relevant, new scientific knowledge that cannot be obtained in any other way;

e) in culturally differentiated communities, including indigenous ones, the prior consent of the community of its own leaders must be counted on, not dispensing, however, efforts to obtain individual consent;

f) when the merits of the research depend on some restriction of information to the subjects, this fact must be duly explained and justified by the researcher and submitted to the Research Ethics Committee. The data obtained from the research subjects may not be used for purposes other than those not provided for in the protocol and/or consent.

V Risks and Benefits

All research involving human beings is considered to involve risk. The eventual damage may be immediate or late, compromising the individual or the community.

V.1 Notwithstanding the potential risks, research involving human beings humans will be admissible when:

a) offer a high possibility of generating knowledge to understand, prevent or alleviate a problem that affects the well-being of research subjects and other individuals;

b) the risk is justified by the importance of the expected benefit;

c) the benefit is greater, or at least equal, to other alternatives already established for prevention, diagnosis and treatment.

V.2 Research without direct benefit to the individual, must provide conditions to be well supported by the research subjects, considering their physical, psychological, social and educational situation.

V.3 The responsible researcher is obliged to suspend the research immediately when perceiving any risk or damage to the health of the subject participating in the research, as a result of the same, not provided for in the consent form. Likewise, as soon as the superiority of one method under study over another is confirmed, the project should be suspended, offering to all subjects the benefits of the best regimen.

V.4 The Research Ethics Committee of the institution must be informed of all adverse effects or relevant facts that alter the normal course of the study.

V.5 The researcher, the sponsor and the institution must assume the responsibility of providing integral assistance to the complications and damages resulting from the foreseen risks.

V.6 The research subjects who suffer any type of damage foreseen or not in the consent term and resulting from their participation, in addition to the right to full assistance, are entitled to compensation.

V.7 The research subject may never be required, under any argument, to waive the right to compensation for damages. The informed consent form must not contain any disclaimer that removes this responsibility or implies that the research subject waives his legal rights, including the right to seek compensation for incidental damages.

VI Research Protocol

The protocol to be submitted for ethical review can only be appreciated if instructed with the following documents, in Portuguese:

VI.1 cover page: project title, name, identity card number, CPF, telephone and mailing address of the responsible researcher and sponsor, name and signatures of the institution and/or organization directors;

VI.2 description of the research, comprising the following items:

a) description of the purposes and hypotheses to be tested;

b) scientific background and data that justify the research. If the purpose is to test a new health product or device, whether of foreign origin or not, the current registration status with regulatory agencies in the country of origin must be indicated;

c) detailed and orderly description of the research project (material and methods, casuistry, expected results and bibliography);
d) critical analysis of risks and benefits;
e) total duration of the research, after approval;
f) explanation of the responsibilities of the researcher, the institution, the promoter and the sponsor;
g) clarification of criteria to suspend or terminate the research;
h) research location: detail the facilities of the services, centers, communities and institutions in which the various stages of the research will be carried out;
i) demonstration of the existence of infrastructure necessary for the development of the research and to deal with eventual problems resulting therefrom, with the documented agreement of the institution;
j) detailed financial budget for the research: resources, sources and destination, as well as the form and amount of the researcher's remuneration;
l) explanation of a pre-existing agreement regarding the ownership of the information generated, demonstrating the inexistence of any restrictive clause regarding the public disclosure of the results, unless it is a case of obtaining a patent; in this case, the results must be made public as soon as the patenting stage is completed;

m) declaration that the research results will be made public, whether favorable or not; and
n) statement on the use and destination of the material and/or data collected.

VI.3 Information regarding the research subject:

a) describe the characteristics of the population to be studied: size, age group, sex, color (IBGE classification), general health status, social classes and groups, etc. Explain the reasons for using vulnerable groups;

b) describe the methods that directly affect the subjects of the research wanted;
c) identify sources of research material, such as specimens, records and data to be obtained from human beings.
Indicate whether this material will be obtained specifically for the purposes of the research or if it will be used for other purposes;
d) describe the plans for the recruitment of individuals and the procedures to be followed. Provide inclusion and exclusion criteria;

e) submit the form or consent form, specific to the research, for consideration by the Ethics Committee in
Research, including information about the circumstances under which consent will be obtained, who will seek to obtain it, and the nature of the information to be provided to research subjects;

f) describe any risk, evaluating its possibility and seriousness.
dade;

g) describe the measures to protect or minimize any possible risk. Where appropriate, describe measures to ensure necessary health care in the event of harm to individuals. Also describe the procedures for monitoring data collection to provide the security of individuals, including measures to protect confidentiality; and

h) present a forecast of reimbursement of expenses to the research subjects. The referring importance cannot be of such an amount that it may interfere with the autonomy of the individual or responsible person's decision to participate or not in the research.

VI.4 qualification of researchers: *Curriculum vitae* of the researcher res
responsible person and the other participants.

VI.5 term of commitment of the responsible researcher and the institution of comply with the terms of this Resolution.

VII Research Ethics Committee (CEP)

All research involving human beings must be submitted to the
tion of a Research Ethics Committee.

VII.1 Institutions in which research involving human beings is carried out must set up one or more than one Research Ethics Committee (CEP), according to their needs.

VII.2 If it is not possible to constitute a CEP, the institution or the responsible researcher must submit the project to the CEP of another institution, preferably among those indicated by the National Research Ethics Committee (CONEP/ MS).

VII.3 Organization – The organization and creation of the CEP will be the responsibility of the institution, respecting the rules of this Resolution, as well as the provision of adequate conditions for its operation.

VII.4 Composition – The CEP must be constituted by a collegiate with a number of not less than 7 (seven) members. Its constitution must include the participation of professionals from the health, exact, social and human sciences, including, for example, jurists, theologians, sociologists, philosophers, bioethicists and at least one member of society representing the institution's users. . It may vary in its composition, depending on the specificities of the institution and the lines of research to be analyzed.

VII.5 It will always have a multi and transdisciplinary character, with no more than half of its members belonging to the same professional category, people of both sexes participating. It can also count on *ad hoc* consultants , people belonging or not to the institution, with the purpose of providing technical subsidies.

VII.6 In the case of research on vulnerable groups, communities and collectivities, a representative should be invited as an *ad hoc* member CEP, to participate in the analysis of the specific project.

VII.7 In research on the indigenous population, a consultant familiar with the customs and traditions of the community must participate.

VII.8 CEP members shall exempt themselves from decision-making when directly involved in the research under analysis.

VII.9 Mandate and choice of members – The composition of each CEP must be defined at the institution's discretion, with at least half of the members with research experience being elected by their peers. The choice of coordination of each Committee must be made by the members that make up the collegiate, during the first working meeting. The term of office will be of three years, with the possibility of reappointment.

VII.10 Remuneration – CEP members cannot be remunerated for the performance of this task, it is recommended, however, that they are exempted from other obligations in the institutions to which they provide service during the Committee's working hours, and may receive reimbursement of expenses carried out with transport, accommodation and food.

VII.11 Archive – The CEP must keep the project, the protocol and the corresponding reports on file for 5 (five) years after the end of the study.

VII.12 Freedom of work – The members of the CEPs must have total independence in making decisions in the exercise of their functions, keeping the information received confidential.
In this way, they cannot suffer any type of pressure from superiors or by those interested in a particular research, they must exempt themselves from financial involvement and must not be subject to a conflict of interest.

VII.13 Responsibilities of the CEP:

a) review all research protocols involving human beings, including multicenter ones, with primary responsibility for decisions on research ethics to be developed in the institution, in order to guarantee and protect the integrity and rights of volunteers participants in said surveys;

b) issue an opinion substantiated in writing, within a maximum period of 30 (thirty) days, clearly identifying the essay, documents studied and revision date. The review of each protocol will culminate in its classification in one of the following categories:
- okay;
- pending: when the Committee considers the protocol to be acceptable, but identifies certain problems in the protocol, the consent form, or both, and recommends a specific review or requests a modification or relevant information, which must be addressed within 60 (six (six) days by the researchers;

- withdrawn: when, after the deadline, the protocol remains pendant;
- not approved; and
- approved and forwarded, with due opinion, for consideration by the National Research Ethics Commission (CONEP/ MS), in the cases provided for in chapter VIII, item 4.c.

c) keep confidential all data obtained in the execution of its task and file the complete protocol, which will be available to the health authorities;

d) monitor the development of projects through annual reports from researchers;

e) play a consultative and educational role, fostering reflection discussion around ethics in science;

f) receive from the research subjects or from any other party reports of abuse or notification of adverse events that may alter the normal course of the study, deciding to continue, modify or suspend the research, and, if necessary, adapt the consent form . Discontinued research without justification accepted by the CEP that approved it is considered unethical;

g) request the institution of an inquiry to the management of the institution in case of reports of irregularities of an ethical nature in the research and, if there is evidence, communicate to the Commission National Research Ethics Committee (CONEP/MS) and, where applicable, to other instances; and

h) maintain regular and permanent communication with CONEP/MS.

VII.14 Action of the CEP:

a) The ethical review of any research proposal involving human beings cannot be dissociated from its scientific analysis. Research that is not accompanied by the respective protocol should not be analyzed by the Committee.

b) Each CEP must prepare its operating rules, containing work methodology, such as: preparation of minutes; annual planning of its activities; frequency of meetings; minimum number of people present to start the meetings;

deadlines for issuing opinions; criteria for requesting consultations from *experts* in the area in which technical information is desired; decision-making model, etc.

VIII National Research Ethics Committee (CONEP/MS)

The National Research Ethics Commission (CONEP/MS) is a collegiate body, of a consultative, deliberative, normative, educational, independent nature, linked to the National Health Council.

The Ministry of Health will adopt the necessary measures for the full functioning of the Commission and its Executive Secretariat.

VIII.1 Composition: CONEP will have a multi and transdisciplinary composition, with people of both sexes and must be composed of 13 (thirteen) full members and their respective substitutes, 5 (five) of which are prominent personalities in the field of ethics in research and in health and 8 (eight) personalities with outstanding performance in the theological, legal and other fields, ensuring that at least one is in the area of health management. Members will be selected from indicative lists prepared by institutions that have CEPs registered with CONEP, 7 (seven) will be chosen by the National Health Council and 6 (six) will be chosen by lot. You can also count on consultants and *ad hoc members,* ensuring the representation of users.

VIII.2 Each CEP may indicate two personalities.

VIII.3 The term of office of CONEP members will be four years with alternating renewal every two years, for seven or six of its members.

VIII.4 CONEP Attributions – CONEP is responsible for examining the ethical aspects of research involving human beings, as well as the adequacy and updating of the relevant standards. CONEP will consult the company whenever it deems it necessary, being responsible, among others, for the following attributions:

a) encourage the creation of institutional CEPs and other bodies;
b) register institutional and other CEPs;
c) approve, within 60 days, and monitor research protocols in special thematic areas such as:
- human genetics;
- human Reproduction;
- new drugs, medicines, vaccines and diagnostic tests (phases I, II and III) or not registered in the country (even if

phase IV), or when the research concerns its use with modalities, indications, doses or administration routes different from those established, including its use in combinations;

- equipment, supplies and health devices that are new or not registered in the country;
- new procedures not yet established in the literature;
- indigenous populations;
- projects involving biosafety aspects;
- research coordinated from abroad or with foreign participation and research involving the shipment of biological material abroad; and

- projects that, at the discretion of the CEP, duly justified, are deemed worthy of analysis by CONEP;

d) provide specific norms in the field of research ethics, including in special thematic areas, as well as recommendations for their application;

e) to function as the final instance of appeals, based on information provided systematically, ex-officio or based on complaints or requests from interested parties, and must express an opinion within a period not exceeding 60 (sixty) days;

f) review responsibilities, prohibit or interrupt research, definitively or temporarily, and may request protocols for ethical review, including those already approved by the CEP;

g) establish an information system and follow-up of the ethical aspects of research involving human beings throughout the national territory, keeping the databases up to date;

h) inform and advise the Ministry of Health, the CNS and other instances of the SUS, as well as the government and society, on ethical issues related to research on human beings;

i) disclose this and other norms related to ethics in research involved I sell human beings;

j) CONEP, together with other sectors of the Ministry of Health, will establish norms and criteria for the accreditation of Research Centers. This accreditation must be proposed by the sectors of the Ministry of Health, according to their needs, and approved by the National Health Council; and

l) establish its own operating rules.

VIII.5 CONEP will submit to the CNS for its deliberation:

a) proposals for general standards to be applied to research involving human beings, including modifications to this standard;

b) annual work plan;

c) annual report of its activities, including a summary of the CEPs established and the projects analyzed.

IX Operationalization

IX.1 Each and every research project involving human beings must comply with the recommendations of this Resolution and the documents endorsed in its preamble. The researcher's responsibility cannot be delegated, cannot be declined, and includes ethical and legal aspects.

IX.2 The researcher is responsible for:

a) present the protocol, duly instructed to the CEP, waiting for its pronouncement, before starting the research;
b) develop the project as outlined;
c) prepare and present partial and final reports;
d) submit data requested by the CEP, at any time;
e) keep in a file, under its custody, for 5 years, the research data, containing individual files and all other documents recommended by the CEP;
f) forward the results for publication, with due credit to the associated researchers and technical personnel participating in the project;

g) justify, before the CEP, interruption of the project or non-publication cation of results.

IX.3 The Institutional Research Ethics Committee must be registered with CONEP/MS.

IX.4 Once the project is approved, the CEP becomes co-responsible for the ethical aspects of the research.

IX.5 Projects approved by the CEP are considered authorized for execution, except those that fall into special thematic areas, which, after approval by the institutional CEP, must be sent to CONEP/MS, which will give the proper referral.

IX.6 Research with new drugs, vaccines, diagnostic tests, equipment and devices for health must be forwarded from the CEP to CONEP/MS and from there, after an opinion, to the Health Surveillance Secretariat.

IX.7 Research funding agencies and the editorial board of scientific journals must require documentation to prove the project's approval by CEP and/or CONEP, when applicable.

IX.8 The institutional CEPs shall send to CONEP/MS, on a quarterly basis, the list of research projects analyzed, approved and concluded, as well as projects in progress and, immediately, those suspended.

X Transitional Provisions

X.1 The Executive Working Group (GET), constituted through Resolution CNS 170/95, will assume the attributions of CONEP until its constitution, being responsible for:

a) take the necessary measures for the process of creating CONEP/MS;

b) establish norms for the registration of institutional CEPs;

X.2 The GET will have 180 days to complete its tasks.

X.3 The CEPs of the institutions must proceed, within 90 (ninety) days, to the survey and analysis, if applicable, of the research projects in human beings already in progress, and must forward them to CONEP/MS, their relationship.

X.4 Resolution 01/88 is hereby revoked.

Adib D. Jatene
President of the National Health Council

I ratify CNS Resolution No. 196, of October 10, 1996, under the terms of the Delegation of Competence Decree, of November 12, 1991.

Adib D. Jatene
Minister of State for Health

Resolution No. 240

NATIONAL HEALTH COUNCIL

Resolution No. 240, of June 5, 1997

The Plenary of the National Health Council at its Sixty-sixth Ordinary Meeting, held on June 4 and 5, 1997, in the exercise of its regimental powers and attributions conferred by Law No. 8080, of September 19, 1990, and by Law No. 8,142, of December 28, 1990, and considering the need to define the term “users” for the purpose of participating in the Research Ethics Committees of the institutions, as determined by Res. CNS 196/96, item VII.4, Resolves that:

- A broad interpretation is applied to the term “users”, contemplating multiple collectivities, which benefit from the work developed by the institution.
- User representatives are people capable of expressing the points of view and interests of individuals and/or groups subject to research at a given institution and who are representative of collective interests and diverse audiences.
- In reference institutions for specific publics or pathologies, representatives of “users” must necessarily belong to the unit's target population or to an organized group that defends their rights.
- In places where there are forums or councils of entities representing users and/or people with pathologies and disabilities, it is up to these instances to appoint the representatives of users in the Ethics Committees.
- The indication of user representatives' names for the Research Ethics Committees must be informed to the corresponding Municipal Council.

Carlos Cesar S. of Albuquerque
President of the National Health Council

I ratify CNS Resolution No. 240, of June 5, 1997, pursuant to the Delegation of Competence Decree, of November 12, 1991.

Carlos Cesar S. of Albuquerque
Minister of State for Health

Resolution No. 251

NATIONAL HEALTH COUNCIL

Resolution No. 251, of August 7, 1997

Plenary of the National Health Council at its Fifteenth Meeting Extraordinary, held on August 5, 1997, in the use of its regimental powers and attributions conferred by Law No. 8,080, of September 19, 1990, and by Law No. 8,142, of December 28, 1990, Solves:

Approve the following standards for research involving human beings for the thematic area of research with new drugs, medicines, vaccines and diagnostic tests:

Preamble

I.1 This Resolution incorporates all the provisions contained in Resolution 196/96 of the National Health Council, on Regulatory Guidelines and Norms for Research Involving Human Beings, of which this is a complementary part of the specific thematic area of research with new drugs, medicines , vaccines and diagnostic tests.

I.2 It also refers to the Resolution of the Common Market Group (GMC) No. 129/96, of which Brazil is a signatory, which provides for technical regulations on the verification of good clinical research practices.

I.3 The rules, resolutions and regulations issued by the SVS/MS must be obeyed, subject to its authorization for execution and subsequent monitoring and control, the technical development of Clinical Pharmacology research projects (Phases I, II, III and IV of products not registered in the country) and Bioavailability and Bioequivalence. Research projects in this area must comply with the provisions of Law No. 6,360 (September 23, 1976) regulated by Decree No. 79,094 (January 5, 1977).

I.4 In any clinical trial and particularly in conflicts of interest involved in research with new products, the dignity and well-being of the subject included in the research must prevail over other interests, whether economic, scientific or community.

I.5 It is essential that all research in the thematic area must be based on standards and scientifically established knowledge in laboratory and *in vitro* experiments and knowledge of the relevant literature.

I.6 It is necessary that the investigation of new products be justified and that they effectively lead to significant advances in relation to the existing ones.

II Terms and Definitions

II.1 Research with new drugs, medicines, vaccines or diagnostic tests - refers to research with these types of products in phase I, II or III, or not registered in the country, even if phase IV when the research is related to its use with modalities, indications, doses or routes of administration different from those established when the registration was authorized, including their use in combinations, as well as bioavailability and/or bioequivalence studies.

II.2 The following terms contained in the Resolution of the Common Market Group (GMC No. 129/96) are incorporated, becoming part of this Resolution:

Phase I

It is the first study in human beings in small groups of volunteers, generally healthy, of a new active principle, or new formulation, generally researched in volunteers. These investigations are intended to establish a preliminary evolution of the safety and pharmacokinetic profile and, when possible, a pharmacodynamic profile.

Phase II - Pilot Therapeutic Study

The objectives of the Pilot Therapeutic Study aim to demonstrate the activity and establish the short-term safety of the active ingredient in patients affected by a specific disease or pathological condition. Surveys are carried out on a limited (small) number of people and are often followed by a management study. It should also be possible to establish dose-response relationships, in order to obtain a solid background for the description of expanded therapeutic studies (Phase III).

Phase III

Expanded Therapeutic Study

These are studies carried out in large and varied groups of patients, with the aim of determining:

- the short- and long-term risk/benefit result of active ingredient formulations;
- globally (generally) the relative therapeutic value.

In this phase, the type and profile of the most frequent adverse reactions are explored, as well as special characteristics of the drug and/or medicinal specialty, for example: clinically relevant interactions, main modifying factors of the effect, such as age, etc.

Phase IV

These are surveys carried out after the product and/or specific cialidade medicinal.

These searches are performed based on the characteristics with which the drug and/or medicinal specialty was authorized. These are usually post-marketing surveillance studies to establish therapeutic value, the emergence of new adverse reactions and/or confirmation of the frequency of occurrence of known adverse reactions, and treatment strategies.

In Phase IV research, the same ethical and scientific standards applied to research in previous phases must be followed.

After a drug and/or medicinal specialty has been marketed, clinical research developed to explore new indications, new methods of administration or new combinations (associations), etc. are considered as research for a new drug and/or medicinal specialty.

Pharmacokinetics

In general, they are all the modifications that a biological system produces in an active principle.

Operationally, it is the study of the kinetics (quantitative relationship between the independent variable time and the dependent variable concentration) of the processes of absorption, distribution, biotransformation and excretion of drugs (active principles and/or their metabolites).

Pharmacodynamics

These are all the modifications that an active ingredient produces in a biological system. From a practical point of view, it is the study of the biochemical and physiological effects of drugs and their mechanisms of action.

Safety margin

Pharmacodynamic indicator that expresses the difference between the toxic dose (eg, LD 50) and the effective dose (eg, ED 50).

Therapeutic Margin

It is the ratio between the maximum tolerated, or also toxic, dose and the therapeutic dose (toxic dose/therapeutic dose). In clinical pharmacology it is used as the equivalent of Therapeutic Index.

III Responsibilities of the Researcher

III.1 The researcher's non-delegable and non-transferable responsibility is reaffirmed under the terms of Resolution 196/96. Likewise, they reaffirm

all responsibilities provided for in the aforementioned Resolution, in particular the guarantee of conditions for the care of the research subjects.

III.2 The responsible researcher must:

a) submit the complete research project to the Research Ethics Committee (CEP), pursuant to Resolution 196/96 and this Resolution.

b) keep on file, respecting confidentiality and secrecy, the forms corresponding to each subject included in the research, for 5 years, after the end of the research.

c) submit a detailed report whenever requested or established by the CEP, the National Research Ethics Commission (CONEP) or the Health Surveillance Secretariat (SVS/MS).

d) communicate to the CEP the occurrence of side effects and/or unexpected adverse reactions.

e) also communicate proposals for possible changes to the project and/or justification for interruption, awaiting the CEP's consideration, except in urgent cases to safeguard the protection of the research subjects, and the CEP must then be communicated a posteriori, at the first opportunity.

f) make available to the CEP, CONEP and SVS/MS all duly required information.

g) to proceed with the continuous analysis of the results, as the research proceeds, with the aim of detecting as early as possible the benefits of one treatment over another or to avoid adverse effects on research subjects.

h) submit periodic reports within the deadlines stipulated by the CEP, with at least a half-yearly report and a final report.

i) give access to the results of exams and treatment to the patient's doctor and/or to the patient himself whenever requested and/or indicated.

J) recommend that the same person not be a research subject in a new project before one year has elapsed from his/her participation in a previous research, unless there can be a direct benefit to the research subject.

IV Research Protocol

IV.1 The protocol must contain all the items referred to in Chap. VI of Resolution 196/96 and also the basic pharmacological information appropriate to the project phase, in compliance with Res. GMC 129/96 – Mercosur – including:

a) specification and rationale of the clinical research phase in which the study will be carried out, demonstrating that previous phases have already been completed.

b) description of the pharmacological substance or product under investigation, including the chemical and/or structural formula and a brief summary of the relevant physical, chemical and pharmaceutical properties. Any structural similarities to other known compounds should also be mentioned.

c) detailed presentation of the pre-clinical information necessary to justify the project phase, containing a report of the experimental studies (materials and methods, animals used, laboratory tests, data referring to pharmacodynamics, safety margin, therapeutic margin, pharmacokinetics and toxicology, in the case of drugs, medications or vaccines). The preclinical results should be accompanied by a discussion as to the relevance of the findings in connection with the expected therapeutic effects and possible undesired effects in humans.

d) data referring to preclinical toxicology comprise the study of acute toxicity, subacute repeated doses and chronic toxicity (repeated doses).

e) toxicity studies must be carried out on at least 3 species of animals, of both sexes, one of which must be non-rodent mammals.

f) in the study of acute toxicity, two routes of administration must be used, one of which must be related to the one recommended for the proposed therapeutic use and the other must be a route that ensures the absorption of the drug.

g) in the study of subacute toxicity, repeated doses and chronic toxicity, the route of administration must be related to the proposed therapeutic use: the duration of the experiment must be at least 24 weeks.

h) in the pre-clinical phase, the toxicity studies must also include the analysis of the effects on fertility, embryotoxicity, mutagenic activity, oncogenic (carcinogenic) potential and other studies, according to the nature of the drug and the therapeutic proposal .

i) according to the importance of the project, in view of the urgency of time, and in the absence of other therapeutic methods, the CEP may approve projects without complying with all phases of clinical pharmacology; in this case there must also be approval from CONEP and SVS/MS.

j) information on the status of research and product registration in the country of origin.

k) presentation of detailed clinical information obtained during the previous phases, related to safety, pharmacodynamics, efficacy, dose-response, observed in studies on human beings, whether healthy volunteers or patients. If possible, each trial should be summarized individually, with description of objectives, design, method, results (safety and efficacy) and conclusions. When

the number of studies is large, summarize in groups by phase to facilitate discussion of results and their implications.

l) justification for the use of placebo and eventual suspension of *washout treatment.*

m) ensure, on the part of the sponsor or, in its absence, on the part of the institution, researcher or promoter, access to the drug under test, in case its superiority in relation to the conventional treatment is proven.

n) in multicenter studies, the researcher should, as far as possible, participate in the design of the project before it begins. If this is not possible, you must declare that you agree with the design already drawn up and that you will follow it.

o) the researcher must receive from the sponsor all the data related to the drug.

p) the financing must not be linked to per payment capita of subjects actually recruited.

q) the protocol must be accompanied by the consent form: in the case of subjects whose capacity for self-determination is not full, in addition to the consent of the legal guardian, the subject's own manifestation must be taken into account, even if with reduced capacity (eg elderly) or undeveloped (eg child).

r) research in psychiatric patients: consent, whenever possible, should be obtained from the patient himself. It is essential that, for each psychiatric patient who is a candidate to participate in the research, the degree of ability to express free and informed consent is established, evaluated by a psychiatric professional who is not a researcher involved in the project.

In the case of drugs with psychopharmacological action, a critical analysis must be carried out regarding the possible risks of creating dependence.

IV.2 Inclusion in the research of healthy subjects:

a) justify the need for its inclusion in the research project and critically analyze the risks involved.

b) describe the forms of recruitment, and there should not be any situation dependency.

c) in the case of drugs with psychopharmacological action, analyze critical the risks of creating dependency.

V CEP assignments

V.1 The CEP will assume with the researcher the co-responsibility for the preservation of ethically correct conduct in the project and in the development of the research, being also responsible for:

a) issue a substantiated opinion appreciating the scientific basis and the adequacy of studies from the previous phases, including pre-clinical ones, with an emphasis on safety, toxicity, adverse reactions or effects, efficacy and results;

b) approve the justification for the use of placebo and *washout;*

c) request partial and final reports from the main researcher, establishing deadlines (at least one semi-annual report) according to the characteristics of the research. Copies of reports must be sent to SVS/MS;

d) in the event that, for the recruitment of research subjects, notices are used in the media, they must be authorized by the CEP. It should not be stated, implicitly or explicitly, that the product under investigation is effective and/or safe or that it is equivalent or better than other existing products;

e) invite research subjects for monitoring and evaluation;

f) request the institution's management to set up an investigation, suspend or interrupt the research, communicating the fact to CONEP and SVS/MS;

g) any indication of fraud or ethical infringement of any nature must lead the CEP to request the installation of a Commission of Inquiry and communicate the results to CONEP, SVS/MS and other bodies (management of the institution, relevant Regional Councils);

h) communicate to CONEP and SVS/MS the occurrence of adverse events you are serious;

i) communicate to the institution the occurrence or existence of problems of administrative responsibility that may interfere with the ethics of the research: then, inform CONEP and SVS/
MS and, if applicable, to the Regional Councils.

V.2 It is delegated to the CEP the approval, from the ethical point of view, of research projects with new drugs, medicines and diagnostic tests, which must, however, be forwarded to CONEP, and to SVS/MS:

a) copy of the substantiated opinion of approval, with the cover sheet filled in;

b) opinion on the partial and final reports of the research;

c) other documents that, eventually, the CEP itself, CONEP or SVS deem necessary.

V.3 In research involving patients undergoing emergency or urgent situations, the CEP will be responsible for previously approving the conditions or limits under which free and informed consent will be given, and the researcher must inform the research subject in due course of his/her participation in the project .

V.4 Assess whether all appropriate measures are being taken, in cases of research on human beings whose capacity for self-determination is or is reduced or limited.

VI Operationalization

VI.1 CONEP will exercise its attributions under the terms of Resolution 196/96, with emphasis on the following activities:

a) Organizing, based on data provided by the CEPs (substantiated opinion of approval, cover sheet duly filled in, partial and final reports, etc.), the information and monitoring system (item VIII.9.g, of Resolution 196 /96).

b) Organize a system for evaluating and monitoring the activities of the CEPs. Such a system, which should also serve for the exchange of information and for the exchange of experiences between the CEPs, will be governed by specific CONEP rules, having, however, the characteristic of inter-peer action, that is, carried out by members of the various CEPs. , with a report to CONEP.

c) Communicate to the competent authorities, in particular the Secretary of Sanitary Surveillance/MS, for the appropriate measures, the cases of ethical infraction found in the execution of the research projects.

d) Provide the necessary information to the bodies of the Ministry of Health, in particular the Health Surveillance Secretariat, for the full exercise of their respective attributions, with regard to the research covered by this Resolution.

VI.2 The Health Surveillance Secretariat/MS will exercise its duties under the terms of Resolution 196/96, with emphasis on the following activities:

a) Communicate, in writing, to CONEP any evidence of violations of an ethical nature that are observed or detected during the execution of the research projects covered by this Resolution.

b) Provide, when requested or deemed relevant, the information necessary for the full exercise of CONEP's attributions.

c) In cases of research involving situations for which there is no established treatment (“humanitarian use” or “out of compassion”), the release of the product may be authorized, on an emergency basis, provided that it has been approved by the CEP, ratified by CONEP and SVS/MS.

d) Standardize its internal operating procedures, aiming at the effective sanitary control of the products object of clinical research.

Carlos Cesar S. of Albuquerque
Minister of State for Health

I ratify CNS Resolution No. 251, of August 7, 1997, under the terms of the Delegation of Competence Decree, of November 12, 1991.

Carlos Cesar S. of Albuquerque
President of the National Health Council

Resolution No. 292

NATIONAL HEALTH COUNCIL

Resolution No. 292, of July 8, 1999

The Plenary of the National Health Council at its Eighty-eighth Ordinary Meeting, held on July 7 and 8, 1999, in the use of its regimental powers and attributions conferred by Law No. 8080, of September 19, 1990, and by Law No. 8,142, of December 28, 1990, and *Considering* the need for complementary regulation of CNS Resolution No.
196/96 (Regulatory Guidelines and Norms for Research Involving Human Beings), attribution of CONEP according to item VIII.4.d of the same Resolution, with regard to the special thematic area "research coordinated from abroad or with foreign participation and research involving shipment of biological material abroad" (item VIII.4.c.8), Decides to approve the following rule:

Definition

Research coordinated from abroad or with foreign participation is considered to be those that involve, in their promotion and/or execution:

a) the collaboration of foreign individuals or legal entities, whether public or private;
b) sending and/or receiving biological materials from the human;
c) sending and/or receiving data and information collected for aggregation in research results;
d) international multicenter studies.

I.1 Subject to the above conditions, they are not included in this area theme:

a) research entirely carried out in the country by a foreign researcher who belongs to the technical staff of a national entity;
b) research developed by a multinational based in the country.

II In all investigations one must:

II.1 prove Brazilian participation and identify the researcher and institute co-responsible national tution;

II.2 explain the responsibilities, rights and obligations, through agreement between the parties involved.

III This Resolution incorporates all the provisions contained in Resolution No. 196/96 of the National Health Council, on Regulatory Guidelines and Norms for Research Involving Human Beings, of which this is a complementary part of the specific thematic area.

III.1 CNS Resolutions referring to other thematic areas simultaneously contemplated in the research, must be complied with, where applicable.

IV The burdens and benefits arising from the investigation process and the research results must be fairly distributed among the parties involved and must be explained in the protocol.

V The researcher and the national institution must be aware of the rules and legal provisions regarding the shipment of material abroad and those that protect industrial property and/or technological transfer (Law No. 9,279, of 5/14/96, which regulates rights and obligations related to industrial property, Decree No. 2,553/98 that regulates it and Law No. 9,610/98 on copyright), explaining, when applicable, the agreements established, in addition to the legal rules in force on the remittance of biological material to the outside.

VI During the course of the research, sponsors and researchers must communicate to the Research Ethics Committees (CEP), relevant information of public interest, regardless of the periodic reports provided.

VII When preparing the protocol, special care must be taken to present the following items:

VII.1 Approval document issued by the Research Ethics Committee or equivalent from an institution in the country of origin, which will promote or also execute the project.

VII.2 When the development of the project in the country of origin is not foreseen, the justification must be placed in the protocol for consideration by the CEP of the Brazilian institution.

VII.3 Details of the financial resources involved: sources (if international and foreign and if there is a national/institutional counterpart), form and amount of remuneration of the researcher and other human resources, expenses with infrastructure and impact on the routine of the health service of the institution where it will take place. It should be avoided, as far as possible, that the contribution of financial resources creates situations of discrimination between professionals and/or users, since these resources can lead to extraordinary benefits for the participants and subjects of the research.

VII.4 Declaration by the promoter or sponsor, if any, of commitment to comply with the terms of the CNS resolutions regarding ethics in research involving human beings.

VII.5 Declaration of the use of the biological material and of the data and information collected exclusively for the purposes foreseen in the protocol, of all those who will handle the material.

VII.6 Researcher's opinion on the protocol, if it was impossible for him to participate in the project design.

VIII Within the attributions provided for in item VIII.4.c.8 of Resolution No. 196/96, it is up to CONEP, after approval by the institutional CEP, to assess research within this thematic area, even if they are simultaneously framed in others.

VIII.1 The omitted cases, referring to the ethical aspects of the research, will be resolved by the National Commission of Ethics in Research.

José Serra
President of the National Health Council

I ratify CNS Resolution No. 292, of July 8, 1999, under the terms of Decree of Delegation of Competence, of November 12, 1991.

José Serra
Minister of State for Health

Resolution No. 303

NATIONAL HEALTH COUNCIL

Resolution No. 303, of July 6, 2000

The Plenary of the National Health Council, at its Ninety-ninth Ordinary Meeting, held on July 5 and 6, 2000, in the use of its regimental powers and attributions conferred by Law No. 8,080, of September 19, 1990, and by Law No. 8,142, of December 28, 1990, and Considering:

- The need for complementary regulation of CNS Resolution No. 196/96 (Regulatory Guidelines and Norms for Research Involving Human Beings), attribution of CONEP according to item VIII.4.d of the same Resolution, with regard to the special thematic area " human reproduction" (item VIII.4.c.2), resolves to approve the following rule:

I Definition: Researches in Human Reproduction are those that are concerned with the functioning of the reproductive system, procreation and factors that affect the reproductive health of the human person.

II In research with intervention in:

- Assisted reproduction;
- Contraception;
- Manipulation of Gametes, Pre-embryos, Embryos and Fetus;
- Fetal Medicine.

The CEP must examine the protocol, prepare the substantiated Opinion and forward both to CONEP with the complete documentation in accordance with CNS Resolution No. 196/96, items VII.13.a, b; VIII.4.c.2.

CONEP will be responsible for final approval of these protocols.

III The approval of research involving other areas of human reproduction is delegated to the CEP.

IV In research on Human Reproduction, all those who are affected by the procedures of the same will be considered "subjects of the research".

V This Resolution incorporates all the provisions contained in CNS Resolution 196/96, of which it is a complementary part, and in other CNS resolutions referring to other thematic areas, simultaneously contemplated in the research, which must be complied with as appropriate.

José Serra
President of the National Health Council

I ratify CNS Resolution No. 303, of July 6, 2000, under the terms of Decree of Delegation of Competence, of November 12, 1991.

José Serra
Minister of State for Health

Resolution No. 304

NATIONAL HEALTH COUNCIL

Resolution No. 304, of August 9, 2000

The Plenary of the National Health Council, at its 100th Ordinary Meeting, held on August 9 and 10, 2000, in the use of its regimental powers and attributions conferred by Law No. 8,080, of September 19, 1990, and by Law No. 8,142, of December 28, 1990, and Considering:

- The need for complementary regulation of CNS Resolution No. 196/96 (Regulatory Guidelines and Norms for Research Involving Human Beings), attribution of CONEP according to item VIII.4.d of the same Resolution, with regard to the special thematic area " indigenous populations" (item VIII.4.c.6).

Resolve:

. Approve the following Norms for Research Involving Human Beings - Indigenous Peoples Area.

Preamble

The present resolution seeks to affirm the due respect for the rights of indigenous peoples with regard to the theoretical and practical development of research on human beings that involve the life, territories, cultures and natural resources of the indigenous peoples of Brazil. It also recognizes the right of indigenous people to participate in decisions that affect them.

These norms incorporate the guidelines already provided for in Resolution 196/96, of the National Health Council, and are based on the main international documents on human rights of the UN, in particular Convention 169 on Indigenous and Tribal Peoples in Independent Countries and Resolution on the ILO (International Labor Organization) Action Concerning Indigenous and Tribal Peoples, of 1989, the Constitution of the Federative Republic of Brazil (Title VIII, Chapter VIII On Indians) and all national legislation supporting and respecting the rights of peoples indigenous people as individual and collective research subjects.

Research involving indigenous communities or individuals must correspond and meet the ethical and scientific requirements indicated in Res. CNS 196/96, which contains guidelines and regulatory norms for research involving human beings and their complementary ones. In particular, attention must also be paid to the

CNS Resolution 292/99 on research with foreign cooperation, in addition to other CNS resolutions on research ethics, Decrees 86,715, of 12/10/81, and 96,830, of 1/15/90, which regulate the temporary visa for foreigners .

II Terms and Definitions

This resolution adopts the following definitions within its scope:

II.1 Indigenous Peoples – peoples with their own organizations and identities, due to the awareness of their historical continuity as pre-Columbian societies.

II.2 Indigenous – who considers themselves to belong to an indigenous community and is recognized by it as a member.

II.3 Isolated Indians – individuals or groups that avoid or are not in contact with the surrounding society.

III Ethical Aspects of research involving indigenous peoples

Research involving indigenous peoples must also comply with bioethical references, considering the peculiarities of each people and/or community.

III.1 The benefits and advantages resulting from the development of research must meet the needs of individuals or groups targeted by the study or similar societies and/or national society, taking into account the promotion and maintenance of well-being, the conservation and protection of biological and cultural diversity, individual and collective health and the contribution to the development of its own knowledge and technology

III.2 Any research involving the indigenous person or his or her community ity must:

III.2.1 respect the world view, customs, aesthetic attitudes, religious beliefs, social organization, peculiar philosophies, linguistic differences and political structure;

III.2.2 not allow physical, mental, psychological or intellectual exploitation and social life of indigenous people;

III.2.3 not admit situations that jeopardize the integrity and physical, mental and social well-being;

III.2.4 have the agreement of the target community of the research that can be obtained through the respective indi- vidual organizations

genas or local councils, without prejudice to individual consent, which, in common agreement with the aforementioned communities, will designate the intermediary for the contact between the researcher and the community. In research in the health area, the District Council must be communicated;

III.2.5 ensure equal consideration of the interests involved, taking into account the vulnerability of the group in question.

III.3 It is recommended, preferably, not to carry out research in communities of isolated Indians. In special cases, detailed justifications must be provided.

III.4 The patenting by others of chemical products and biological material of any nature obtained from research with indigenous peoples will be considered ethically unacceptable.

III.5 The formation of DNA banks, cell lines or any other biological material related to indigenous peoples is not allowed without the express agreement of the community involved, without the detailed presentation of the proposal in the research protocol to be submitted to the Research Ethics Committee (CEP) and the National Research Ethics Committee (CONEP) and the formal approval of the CEP and CONEP;

III.6 Non-compliance with any of the above items must be communicated to the institutional CEP and to CONEP of the National Health Council, for the appropriate measures.

IV The research protocol

The protocol to be submitted for ethical evaluation must comply with item VI of the Resolution 196/96, adding:

IV.1 Commitment to obtain consent from the communities involved as provided for in item III • 2 of this standard, describing the process for obtaining consent.

IV.2 Description of the process of obtaining and registering the Free and Informed Consent Term (ICF), ensuring the adequacy to the cultural and linguistic peculiarities of those involved.

V Protection

V.1 The research may be suspended at any time, subject to the provisions of item III.3.z of Resolution 196/96, provided that:

V.1.1 its interruption is requested by the indigenous community under study;

V.1.2 the research in development will generate conflicts and/or any type of discomfort within the community;

V.1.3 there is a violation in the forms of organization and survival of the indigenous community, mainly related to the life of the subjects, human resources, plant genetic resources, knowledge of the properties of the soil, subsoil, fauna and flora, oral traditions and the all the artistic expressions of that community.

VI Attributions of CONEP

VI.1 Within the attributions provided for in item VIII.4.c.6 of Resolution CNS 196/96, it is up to CONEP, after approval by the institutional CEP, to appreciate the research in this thematic area, even if it is simultaneously included in another .

VI.2 Opinion of the Indian Intersectoral Health Commission (CISI), when consulting is required, may be requested by CONEP.

VI.3 Omissions regarding the ethical aspects of the research will be resolved by the National Research Ethics Commission.

José Serra
President of the National Health Council

I ratify CNS Resolution No. 304, of August 10, 2000, under the terms of the Delegation of Competence Decree, of November 12, 1991.

José Serra
Minister of State for Health

Resolution No. 340

NATIONAL HEALTH COUNCIL

Resolution No. 340, of July 8, 2004

The Plenary of the National Health Council, at its one hundred and forty-fourth Ordinary Meeting, held on July 7 and 8, 2004, in the use of its regimental powers and attributions conferred by Law No. 8,080, of September 19, 1990 , and by Law No. 8,142, of December 28, 1990, and

Considering the recent technical-scientific advance and its applications in research in human genetics, demanding positioning of institutions, researchers and Research Ethics Committees (CEP) throughout the country, demanding, therefore, complementary regulation to CNS Resolution No. 196 /96 (Regulatory Guidelines and Norms for Research Involving Human Beings), attribution of the National Research Ethics Commission (Conep), according to item VIII.4 of that Resolution;

Considering the subsidies coming from the CEPs – Conep system and the experience accumulated in the analysis of research projects in this area so far; and

Considering the need to consider potential health risks and the protection of human rights, fundamental freedoms and respect for human dignity in the collection, processing, use and storage of human genetic data and materials,

Resolve:

Approve the following Guidelines for Ethical Analysis and Processing of Projects Research papers in the Special Thematic Area of Human Genetics:

Preamble:

This Resolution incorporates all the provisions contained in CNS Resolution No. 196/96 of the National Health Council, on Regulatory Guidelines and Norms for Research Involving Human Beings, of which this is a complementary part of the specific thematic area, and also incorporates , where applicable, the provisions contained in CNS Resolutions No. 251/97, 292/99 , 303/2000 and 304/2000.

II Terms and Definitions:

II.1 Research in human genetics involves the production of genetic or proteomic data on human beings, which may take several forms:

a) research on basic genetic mechanisms: studies on the location, structure, function and expression of human genes and chromosomal organization;

b) research in clinical genetics: research that consists of the descriptive study of individuals individually and/or in their families, aiming to elucidate certain conditions of probable genetic etiology, which may involve analysis of clinical information and tests of genetic material;

c) research in population genetics: studies of normal or pathological genetic variability in groups of individuals and the relationship between these groups and a particular condition;

d) human molecular research: research involving molecular tests associated or not with diseases; genetic or epigenetic studies of nucleic acids (DNA and RNA) or proteins aiming at new treatments or prevention of genetic disorders, other pathologies or the identification of molecular variability;

e) gene and cell therapy research: introduction of recombinant DNA or RNA molecules into human somatic cells *in vivo* (in vivo gene therapy) or human somatic cells *in vitro* and subsequent transference of these cells to the organism (ex *vivo* gene therapy) and research with human stem cells with genetic modifications; and

f) research in behavioral genetics: study with the objective of establishing possible relationships between genetic characteristics and human behavior.

II.2 Any procedure related to human genetics, whose acceptance is not yet established in the scientific literature, will be considered research and, therefore, must comply with the guidelines of this Resolution. Genetic procedures in assisted reproduction are included, not regulated by the Federal Council of Medicine.

III Ethical Aspects:

The main purpose of genetic research must be related to the accumulation of scientific knowledge that allows to alleviate suffering and improve the health of individuals and humanity.

III.1 Genetic research produces a special category of data as it contains medical, scientific and personal information and must therefore be evaluated.

the impact of their knowledge on the individual, the family and the totality of the group to which the individual belongs.

III.2 Data protection mechanisms must be foreseen in order to avoid stigmatization and discrimination against individuals, families or groups.

III.3 Research involving predictive tests must be preceded, before collecting the material, with clarifications on the meaning and possible use of the predicted results.

III.4 Research subjects must be offered the option of choosing between to be informed or not about the results of their exams.

III.5 Research projects must be accompanied by a proposal for genetic counseling, when applicable.

III.6 It is up to the research subjects to authorize or not the storage of data and materials collected within the scope of the research, after being informed of the procedures defined in the Resolution on the storage of biological materials.

III.7 Every individual may have access to their genetic data, as well as the right to withdraw them from banks where they are stored, at any time.

III.8 In order for individual genetic data to be irreversibly dissociated from any identifiable individual, a justification for such a procedure must be presented for evaluation by the CEP and Conep.

III.9 In cases of approval of disassociation of genetic data by CEP and Conep, there must be clarification to the research subject about the advantages and disadvantages of dissociation and a specific Consent Term for this purpose.

III.10 Item V.7 of CNS Resolution No. 196/96 must be observed, including with regard to possible patent registration.

III.11 Genetic data resulting from research associated with an identifiable individual may not be disclosed or accessible to third parties, notably employers, insurance companies and educational institutions, and must not be provided for cross-referencing with other data stored for judicial or other purposes, unless consent is obtained from the research subject.

III.12 Human genetic data collected in research with a specific purpose may only be used for other purposes if the prior consent of the donor or its legal representative is obtained and through the elaboration of a new research protocol, with the approval of the Ethics Committee in Research and, if applicable, Conep. In cases where it is not possible to obtain the informed consent, a justification must be presented for consideration by the CEP.

III.13 When there is a flow of human genetic data between institutions, an agreement must be established between them in order to favor cooperation and equitable access to data.

III.14 Human genetic data must not be stored by an individual, requiring the participation of a reputable responsible institution that guarantees adequate protection.

III.15 The benefits of using human genetic data collected within the scope of research, including population genetics studies, must be shared among the community involved, international or national, as a whole.

III.16 Research with intervention for modification of the human genome can only be carried out in somatic cells.

IV Research Protocol:

IV.1 Research in the area of human genetics must be submitted to the CEP and, when applicable, to Conep as complete protocols, in accordance with Chapter VI of CNS Resolution No. 196/96, not being accepted as amendment, addendum or protocol sub-study of another area, and must also include:

a) research justification;

b) how the genes/segments of DNA or RNA or gene products under study are related to the eventual condition of the research subject;

c) clear explanation of the exams and tests that will be performed and indication of the genes/DNA or RNA segments or gene products that will be studied;

d) justification for the choice and size of the sample, particularly when dealing with a vulnerable population or group and with differentiated cultures (indigenous groups, for example);

e) ways of recruiting research subjects and controls, when applicable;

f) careful analysis of current and potential risks and benefits for the individual, the group and future generations, when applicable;

g) information regarding the use, storage or other destinations of the biological material;

h) measures and care to ensure privacy and avoid any type or situation of stigmatization and discrimination of the research subject, the family and the group;

i) explanation of a pre-existing agreement regarding the ownership of the information generated and regarding industrial property, when applicable;

j) description of the genetic counseling and clinical follow-up plan, when indicated, including names and contacts of the responsible professionals, type of approach according to expected situations, consequences for the subjects and expected conduct. Professionals responsible for genetic counseling and clinical follow-up must have the professional training and qualifications required by professional councils and specialist societies;

l) justification for sending the biological material and/or data obtained to other institutions, national or abroad, with a clear indication of the type of material and/or data, as well as the list of exams and tests to be performed. Clarify the reasons why the exams or tests cannot be performed in Brazil, when applicable; and

m) in international cooperative projects, description of opportunities technology transfer data.

V Free and Informed Consent Term (FICT):

V.1 The TCLE must be prepared in accordance with the provisions of Chapter IV of CNS Resolution No. 196/96, with a special focus on the following items:

a) clear explanation of the exams and tests that will be performed, indication of the genes/DNA or RNA segments or gene products that will be studied and their relationship with the eventual condition of the research subject;

b) guarantee of secrecy, privacy and, when applicable, anonymity;

c) genetic counseling and clinical follow-up plan, with the indication of those responsible, at no cost to the research subjects;

d) type and degree of access to the results by the subject, with the option of knowing or not knowing this information;

e) in the case of material storage, the information must be included in the TCLE, explaining the possibility of being used in a new research project. It is also essential to state that the subject will be contacted to grant or not authorization to use the material in future projects and that, when this is not possible, the fact will be justified to the CEP. Also explain that the material will only be used upon approval of the new project by CEP and Conep (when applicable);

f) information regarding individual data protection measures, exam and test results, as well as the medical record, which will only be accessible to the researchers involved and access to third parties (insurers, employers, hierarchical supervisors, etc.) will not be allowed.);

g) information regarding protection measures against any type of discrimination and/or stigmatization, individual or collective; and

h) in family investigations, the Free and Informed Consent Form of each individual studied must be obtained.

VI Operationalization:

VI.1 It is incumbent upon the CEP, in accordance with the provisions of Chapter VII of CNS Resolution No. 196/96, to analyze research projects, assuming co-responsibility with regard to ethical aspects.

VI.2 It is up to the CEP to immediately return to the researcher the protocol that does not contain all the relevant information (chapter VI – CNS Resolution no. 196/96, as well as those referred to in chapters III and IV of this Resolution).

VI.3 Conep is responsible for final approval of research in human genetics that includes:

a) sending abroad genetic material or any human biological material to obtain genetic material;

b) storage of biological material or human genetic data abroad and in the country, when in agreement with foreign institutions or in commercial institutions;

c) alterations in the genetic structure of human cells for use tion *in vivo;*

d) research in the field of human reproduction genetics (reproge netics);

e) research in behavioral genetics; and
f) research in which the irreversible dissociation of data from research subjects is foreseen.

VI.4 In the cases provided for in item VI.3 above, the CEP must examine the protocol, prepare the substantiated opinion and send both to Conep with the complete documentation in accordance with CNS Resolution No. 196/96, items VII.13. a and b VIII.4.c.1. The researcher must be informed that he/she will have to wait for Conep's opinion to start executing the project.

VI.5 The final approval of human genetics projects that do not fit into item VI.3 above is delegated to the CEP. In these cases, the CEP must send Conep the cover page and the final substantiating opinion, whether approval or non-approval.

VI.6 The shipment of material abroad must comply with the regulatory and legal provisions of the country.

HUMBERTO COSTA
President of the National Health Council

I ratify CNS Resolution No. 340, of July 8, 2004, under the terms of Decree of Delegation of Competence of November 12, 1991.

HUMBERTO COSTA
Minister of State for Health

Resolution No. 346

NATIONAL HEALTH COUNCIL

Resolution No. 346, of January 13, 2005

The Plenary of the National Health Council at its Hundredth Fifth Ordinary Meeting, held on January 11, 12 and 13, 2005, in the use of its regimental powers and attributions conferred by Law No. 8,080, of September 19, 1990, and by Law nº 8.142, of December 28, 1990, and considering the experience accumulated in the National Commission of Ethics in Research CONEP in the appreciation of multicenter research projects and aiming at a simplified procedure, establishes the following regulation for processing multicenter research projects in the CEPs Research Ethics Committees – CONEP system.

RESOLVE:

I- Definition of the term:

Multicenter projects – research project to be conducted according to a single protocol in several research centers and, therefore, to be carried out by a responsible researcher at each center, who will follow the same procedures.

II- Processing of multicenter research protocols:

The multicenter research protocols that must receive an opinion from the CONEP, pursuant to CNS Resolution No. 196/96 and its complementary ones, will proceed as follows:

1. Only the first protocol, sent by one of the centers, will be analyzed by CONEP. The list of centers involved must accompany the protocol and the CEP's substantiated opinion. CONEP, after any pending issues have been resolved, will send the final opinion to this CEP and to the other centers involved;

a) In case there is a national research coordinator, the CEP to initially receive the protocol and send it to CONEP must be the CEP of the institution to which it belongs or, according to CNS Resolution nº 196/96 item VII.2, the CEP indicated by CONEP;

2. The research protocol not approved by CONEP for the first center cannot be carried out in any center.

3. The research protocol approved by CONEP must be presented by the respective researchers to the CEPs of the other centers, which must require the researcher to attach a declaration that the protocol is identical to that presented to the first center.

a) Any changes or additions referring to responses to the requirements of the CONEP opinion must be presented separately, in a well-identified manner, attached to the protocol after the documents above.

4. CONEP will delegate to the other CEPs the final approval of the projects mentioned in item 3 above, maintaining the prerogative of these CEPs to approve or not the protocol in their institution, always being responsible for:

a) verify the adequacy of the protocol to the institutional conditions and the competence of the responsible researcher at the institution;

b) demand compliance with any changes approved by CONEP and requirements of the CEP itself; and

c) send the substantiated opinion to CONEP, in case of non-approval end in zip code.

5. Only the CEP of the first center will be in charge of notifications to CONEP in case of serious adverse events occurring in foreign centers, interruptions of research or relevant changes, maintaining the necessary notifications of each researcher to the local CEP.

a) in the event of an adverse event occurring in the country, the researcher responsible for the center where it occurred, after analysis, must notify the CEP and the latter, in the event of a serious adverse event, to CONEP.

6. The regulation of 08/08/02 of CNS Resolution No. 292/99, on delegation for research with foreign cooperation, is revoked, maintaining CNS Resolution No. 292/99 of 07/08/99 in its entirety.

HUMBERTO COSTA
President of the National Health Council

I ratify CNS Resolution No. 346, of January 13, 2005, pursuant to the Delegation of Competence Decree of November 12, 1991.

HUMBERTO COSTA
Minister of State for Health

Resolution No. 347

NATIONAL HEALTH COUNCIL

Resolution No. 347, of January 13, 2005

The Plenary of the National Health Council at its 150th Ordinary Meeting, held on January 11, 12 and 13, 2005, in the exercise of its regimental powers and attributions conferred by Law No. 8,080, of September 19, 1990, and by Law No. 8,142, of December 28, 1990, and considering the need to regulate the storage and use of human biological material within the scope of research projects

RESOLVE:

Approve the following guidelines for ethical review of research projects that involve storage of materials or use of materials stored in previous research:

1. When, in research projects, the storage of human biological materials for future investigations is foreseen, in addition to the points provided for in CNS Resolution No. 196/96, the following must be presented:

   1.1. Justification as to the need and opportunity for future uses; 1.2. Consent of research subjects donors of biological material
   gico, authorizing the custody of the material;
   1.3. Declaration that all new research to be carried out with the material will be submitted for approval by the institution's CEP and, when applicable, by the National Research Ethics Commission-CONEP;
   1.4. Standard or regulation prepared by the depositary institution for the storage of human biological materials.

2. The biological material will be stored under the responsibility of the depositary institution, which must have a rule or regulation approved by the CEP of that institution, which must include: 2.1. Definition of those responsible for custody and authorization of use
   do material;
   2.2. Mechanisms that guarantee secrecy and respect for confidentiality (coding);
   2.3. Mechanisms that ensure the possibility of contacting donors to provide information of interest to them (for example, test results for clinical follow-up or genetic counseling) or to obtain specific consent for use in a new research project;

3. Storage may be authorized for a period of 5 years, when the project is approved by the CEP and, when applicable, by CONEP, and may be renewed at the request of the depositary institution, accompanied by justification and report of the research activities carried out with the material.

4. In the case of research involving more than one institution, there must be an agreement between the participating institutions, contemplating ways of operating and using the stored material.

5. In the case of storage and/or formation of the biological material bank abroad, the legislation in force for the shipment of material abroad must be obeyed, and the regulation must be presented for analysis by the CEP regarding the fulfillment of the requirements of item II.

5.1. The Brazilian researcher and institution must be considered as shareholders of the bank, with the right to access it for future research. Therefore, the stored material cannot be considered as the exclusive property of a country or depositary institution.

6. About using stored samples:

6.1. Stored samples can be used in new research approved by the CEP and, when applicable, by CONEP;

6.2. Research protocols that intend to use stored material nothing should include:

a) Justification for the use of the material;

b) Description of the collection and storage system, with definition start date or period definition;

c) Copy of the Free and Informed Consent Term obtained during the research in which the material was collected, including authorization for storage and possible future use, if the storage occurred from research approved after CNS Resolution No. 196/ 96; and

d) Specific TCLE for new research: in case of impossibility of obtaining specific consent for new research (deceased donor, previous unsuccessful contact attempts or others) the justifications must be presented as part of the protocol for consideration by the CEP, which will waive or not individual consent.

6.3. In the case of biological material for which ANVISA rules are available for storage, they must also be observed.

HUMBERTO COSTA
President of the National Health Council

I ratify CNS Resolution No. 347, of January 13, 2005, pursuant to the Delegation of Competence Decree of November 12, 1991.

HUMBERTO COSTA
Minister of State for Health

MEMBERS OF THE NATIONAL RESEARCH ETHICS COMMISSION / 2005-2007

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