

Ethical regulation of research in Brazil: the role of social control

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Abstract

This work presents historical facts that resulted in the first health research normalization in Brazil and seeks to highlight the importance of social participation in its control. Going through the Regulatory marks of the countries, the social movements were evidently responsible for changes in the system formed by the research ethics committees and by the National Committee of Research Ethics. However, there are hindrances regarding the standards of analysis in the diverse committees, the difficulties of following the projects in course, and the register on the Plataforma Brasil. The Brazilian system is, nonetheless, a referential for other countries regarding respect and protection of research participants and the insertion of society in the committees.

Keywords: Ethics, research. Ethics committees, research. Social control, formal.

Resumo

Regulamentação ética da pesquisa no Brasil: papel do controle social

Este trabalho apresenta fatos históricos que resultaram na primeira normalização de pesquisa em saúde no Brasil e busca salienta a importância da participação social no seu controle. Ao percorrer os marcos regulamentadores do país, é evidente que as movimentações sociais foram responsáveis por mudanças no sistema formado pelos comitês de ética em pesquisa e pela Comissão Nacional de Ética em Pesquisa. Entretanto, existem entraves no que concerne aos padrões de análise nos diversos comitês, às dificuldades de acompanhamento dos projetos em andamento e ao cadastro na Plataforma Brasil. Porém, o sistema brasileiro é referencial para outros países quanto a respeito e proteção de participantes de pesquisa e à inserção da sociedade no âmbito dos comitês.

Palavras-chave: Ética em pesquisa. Comitês de ética em pesquisa. Controle social formal.

Resumen

Regulación ética de la investigación en Brasil: el rol de control social

Este trabajo presenta los hechos históricos que resultaron en la primera regulación de la investigación en salud en Brasil y busca señalar la importancia de la participación social en su control. Los marcos de regulación en el país ponen en evidencia que los movimientos sociales fueron los responsables de los cambios en el sistema conformado por los comités de ética en investigación y la Comisión Nacional de Ética en Investigación. Sin embargo, existen obstáculos con respecto a los estándares de análisis en los diversos comités, a las dificultades de seguimiento de los proyectos en curso y al registro en la Plataforma Brasil. A pesar de esto, el sistema brasileño es una referencia para otros países con relación al respeto y protección de los participantes en investigación y la inclusión de la sociedad en el ámbito de los comités.

Palabras clave: Ética en investigación. Comités de ética en investigación. Control social formal.

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In 2019, the 16th Brazilian National Health Conference (8th+8)¹ revived the historical value of the 8th Conference in the defense of participatory democracy and the foundation of health, which, through the engagement of the health movement, was established as a right in the Federal Constitution of 1988². The political background to the development of the Constitution provided participatory forums at the various levels of public administration. The implementation of decentralizing policies made it possible for the management-related councils to become involved in the decision-making process³. This constitutional framework restructured the Brazilian National Health Council (CNS), formed by representatives of users, managers and workers in healthcare with the aim of facilitating social control and community participation in managing the sector. Despite being part of the organizational structure of the Brazilian Ministry of Health, the CNS has autonomy in its proposals.

The participation of society in the design of health strategies and policies and in the control and evaluation of government action imparted a distinctive feature to the Unified Health System (SUS) that has encouraged and favored the commitment of workers in the area, even in the face of limitations imposed at the three levels of government that generate dissatisfaction in public services. A prominent aspect is the spread of the right to healthcare, visible in the manifestations of citizenship⁴.

The premises resulting from the 8th Conference, especially the expansion of the concept of health and the definition of community participation as a new social order, amid reports of ethical deviations, also led to the enactment of CNS Resolution 1/1988⁵. This document provides health research standards, determining the establishment of ethics committees in research institutions, with at least one user among its members⁵. However, since 2017, Bill 7082/2017⁶, stemming from Senate Bill 200/2015⁷, has been under consideration in the Chamber of Deputies, proposing new provisions on clinical research with humans, as well as the creation of the National System of Ethics in Clinical Research with Humans. The exclusion of social control is among the project's proposals, undermining of the pillars of the current system in Brazil.

Thus, the goal of this work is to present the historical facts that resulted in the first regulation of health research in Brazil and to emphasize the importance of social participation in its control.

Historical background

CNS Resolution 1/1988

A wide range of articles⁸ is readily available describing the global historical background that resulted in the international ethical guidelines adopted in the conduct of research with humans, such as the Nuremberg Code (from 1947)⁹, the *Declaration of Helsinki* (from 1964 and later)¹⁰, the *Belmont Report* (from 1978)¹¹, the International Ethical Guidelines for Health-related Research Involving Humans (from 1982 and later)¹² and the *Universal Declaration on Bioethics and Human Rights* (from 2005)¹³.

The most widely reported context is the experiments carried out by Nazi and Japanese doctors in World War II, which involved infecting prisoners and testing in extreme conditions, such as temperature and altitude¹⁴. Other frequently cited cases were the experiments carried out in a Jewish hospital in New York in 1963, when cancer cells were injected in patients, and the Tuskegee study, conducted between 1940 and 1972 in the US state of Alabama, which monitored the natural history of syphilis in about 600 black persons without offering them penicillin¹⁵. Those events mobilized public opinion on the issue of social control in research involving humans.

According to Fonseca¹⁶, an important factor for the effective beginning of the activities of ethics committees was the consequences of the trials at the Jewish hospital, which attracted negative publicity for evoking Nazi experiments, threatening research funding. Thus, as of 1966, all research funded by the United States government had to be previously approved by a group of experts to ensure the well-being and acceptance of the participants and to strike a balance between the risks and benefits of the investigation¹⁶.

In Brazil, the need for ethical regulation emerges in the 1980s, with CNS expressing interest in the subject. Freitas¹⁷ reports some previous concern on the part of a few research groups, mainly driven by the need to support initiatives by

the pharmaceutical industry, since Brazilians were starting to cooperate in research carried out in countries that already required proof of measures to protect the individuals involved. In addition, cases of ethically questionable research were being disclosed.

An emblematic case of a study that violated ethical standards was the clinical trial of efficacy and safety of Norplant, a long-acting intradermal contraceptive used in Brazil in the 1970s with no registration with a regulatory agency. It was presented as a research project to the University of Campinas in 1984, recruiting 3,562 women between August of that year and January 1986—most of them poor—who entered the study on the recommendation of a doctor or nurse, without informed consent. The research had no inclusion or exclusion criteria. Many participants emigrated to other states due to economic difficulties and the researchers were no longer able to follow up with them or remove the implant. Following complaints of several adverse events, such as unusual menstruation and weight gain, and of the aforementioned irregularities, a committee was created by the Brazilian Ministry of Health, which canceled the protocol in 1986¹⁸.

It should be noted that, according to Freitas, in 1984 the following was included in Chapter II of *Infractions of the Code of Medical Deontology: physicians are prohibited, in the exercise of their profession, from carrying out research with humans without being duly authorized and without the necessary supervision by an Ethics Committee. In the 1988 review of the Code of Medical Ethics, Article 127 endorses the need to “submit the protocol for approval and supervision by a committee that is totally independent of the researcher”*¹⁹.

This context, plus the awareness raised in Brazil, especially among the scientific milieu, by the work *Experimentação com seres humanos* [Experiments with Humans]²⁰, which featured reflections on international cases of great repercussion, is decisive for the enactment of CNS Resolution 1/1988⁵, which starts supervising Brazilian research through the Science and Technology Intersectoral Committee (Cict), determining that health institutions set up research ethics committees (CEP).

Evolution of the ethics regulation system in Brazil: the CEP/Conep System

Notwithstanding the need to regulate research with humans in Brazil, a survey published in 1995²¹, which aimed to verify the operation of CEPs in health institutions, found that only one of them fully complied with CNS Resolution 1/1988⁵ and that projects were being evaluated by medical ethics committees, scientific committees and even by institutional management.

In addition, it was found that new situations and ethical dilemmas were stemming from the advancement of science and international partnerships, with some protocols planned for Brazil that had not been approved in the country of origin, in addition to research projects that became healthcare practice without analysis of results and which hindered evaluation and monitoring by Cict/CNS. Added to that was the system's actual framework at the time, based on accreditation of research centers, which made it difficult to determine the responsibilities of both those directly interested in the research and the authorities in charge of control¹⁷.

This context started leading to situations such as studies with foreign sponsorship and collection of data and materials in the country without the participation of a Brazilian institution, research not approved in the country of origin but which proposed to recruit more vulnerable populations and studies whose risk levels were too high to be offset by the suggested benefits.

Such events corroborated the fact that no strategies had been designed to further the creation of committees or of training programs to understand and execute their functions. The responsibilities of researchers, sponsors and control bodies were not defined and, therefore, many projects were not being submitted to any independent evaluation. The discussion gained momentum within the CNS, which encouraged debates on the topic in *Revista Bioética*²², a journal of the Brazilian Federal Council of Medicine, as well as in other publications of academic institutions. In addition, in 1995 CNS set up a multiple working group with representatives from federations, government agencies and society, clearly defining a policy of social control¹⁷.

Thus began the process of reviewing the previous standards, which considered the following premises: 1) the new standard would be applicable to all projects involving humans; 2) it was recognized that risks and uncertainties are not always predictable and may affect health, involving aspects of physical, psychological and social well-being; 3) updated ethics fundamentals would be used; 4) the final regulation should meet the needs of Brazilian society and, therefore, would be developed with widespread public consultation. This process sought to identify entities and people involved in research with humans, such as scientific associations, universities, research centers and organized civil society groups involved in human rights, and to analyze public policies from a bioethical point of view.

Seminars and debates were organized and encouraged in the institutions and in CNS itself. In addition, in order to expand and include other groups, information was distributed and comments were requested through *Revista Bioética*²² and *SUS Epidemiological Report*²³. The first version of the regulation was introduced at public hearings²⁴, at the I Brazilian Bioethics Congress²⁵ and at the 10th National Health Conference²⁶.

Finally, in 1996, CNS publishes the regulatory guidelines and standards for research involving humans, CNS Resolution 196/1996²⁷. This regulation determines, among other provisions, the accreditation of CEPs with the National Research Ethics Committee (Conep), creating the current CEP/Conep System and establishing a national regulatory framework. CNS Resolution 196/1996²⁷ was based on the bioethical principles of autonomy, beneficence, non-maleficence, justice and equity. However, it is worth noting that none of them possesses absolute value, nor is there any hierarchy between them. According to Freitas and Hossne²⁸, what does have absolute value is the dignity of humans, allied to solidarity. Thus, the creation of the CEP/Conep System can also be seen as an act of humanization, affording visibility to research participants, previously seen as “guinea pigs.”

Following this resolution, CNS starts to issue complementary regulation addressing specific areas that pose greater ethical risk, such as genetics²⁹, fetal medicine³⁰, special populations

like indigenous peoples³¹, research with foreign cooperation³² and formation of banks of biological material³³, among others.

Institutions started to comply with the regulation, accrediting committees, and CEPs and Conep took charge of analyzing protocols in the special areas. This process was a response to society's demand, given the scientific and economic reality, as an expression of the maturity of citizenship in Brazil. Many people engaged in the process. By 2000, 287 institutional CEPs were registered, with around 2 thousand people involved as members, whether healthcare professionals or representatives of users of the system³⁴. Undoubtedly, the identification of conflicts of interest and the prevention of risks to research participants became the system's clear-cut mission.

According to Barbosa and collaborators³⁵, although some institutions invested in the creation of CEPs, their implementation was initially marked by lack of infrastructure and staff shortage, resulting in non-compliance with the 30-day analysis period for issuing opinions provided by CNS Resolution 196/1996²⁷. On the other hand, resistance of research sponsors to the regulation requirements also delayed the conclusion of evaluations, resulting in successive pending issues.

By late 2007 there were 557 CEPs set up in the major Brazilian research centers, comprising more than eight thousand people. Figures from 2005 showed that CEPs evaluated 17,000 projects that year, projected to involve 600,000 volunteers. Conep was reviewing between 1,000 and 1,500 projects a year, which accounted for less than 10% of the system's projects¹⁸.

Achievements of the CEP/Conep System

The evaluation of special area projects by CEPs and Conep, which aimed to apply greater ethical rigor to higher risk research, was a point that, over time, generated criticism of the system for alleged double evaluation and lengthy processing. On the other hand, it made it possible for more complex projects to undergo careful analysis, uninfluenced by sponsors and researchers, guaranteeing independence and allowing monitoring by CEPs, which forwarded to Conep their first opinions on

said projects. Such procedures were gradually discussed, with adaptations on all sides, reaching more acceptable processing terms with procedural solutions, such as project analysis by the coordinating center, with a valid opinion for other participating centers³⁶.

But in addition to those solutions, persistent clashes and debates generated greater compliance with ethical aspects in protocols, such as acknowledgment of the ethical inadequacy of using placebo in situations where there is proven therapy and the responsibility to continue treatments initiated in a research situation if they benefit participating volunteers. Also discussed was the need to carefully identify the vulnerabilities of the population, which included rejecting projects that had not been approved to recruit participants in their country of origin.

Other ethical issues were also raised, especially by Conep—which accumulated experience with special projects—often leading to pending issues regarding necessary modifications. A few cases resulted in the protocol being rejected, such as issues related to the formation of banks of biological material, genetic studies without feedback to patients, transparency and full understanding of the participant's consent process. All these issues were gradually regulated in standards²⁷⁻³³ and such achievements placed Brazil at the forefront of the protection of research volunteers, unlike, for example, in other Latin American countries, which do not have a reasonably independent system of social control in place³⁷.

A case in point was an international project on the use of a new drug, Nevirapine, for the vertical treatment of AIDS. Since 1996, treatment with AZT, which reduced the risk of vertical transmission of the disease to the baby from 28% to 8%, had been available in the public health system. However, the project, already approved in other countries, intended to compare the new treatment with placebo. The institutional CEP that received the protocol for analysis identified the flaw and forwarded ethical questions to Conep. That body requested changes, recommending the exclusion of placebo and comparison with the treatment already approved and available in Brazil. The sponsors offered no new arguments and the protocol was ultimately modified in Brazil, preventing mothers and babies from going

untreated. Unfortunately, in other developing countries where the project had been approved, many were unable to receive this protection, remaining vulnerable³⁸.

Amy Gutmann and James Wagner³⁹ argue that when regulation is necessary, such as the requirement of informed consent and the limitation of risks in research involving humans, ethics education can ensure that rules become true ethical advantages rather than bureaucratic obstacles. They add that when scientists themselves accept ethical responsibility, they minimize the need for complex and costly external regulation.

Other persistent clashes occurred with researchers and sponsors in the field of mental health. Comparative studies with placebo rather than drugs were being conducted in Brazil, claiming to be following requirements from regulatory bodies in the United States, European Union and Japan for the approval of new drugs^{17,18}. Some Brazilian researchers insisted on the scientific need for comparison with placebo, presenting projects that had not been approved in the countries of origin and did not ethically consider the risks to patients in the control groups, resisting Conep's review proposals, especially in situations in which they had already obtained approval from institutional CEPs^{17,18}. They even blamed the system for the stagnation and decline of Brazilian technical-scientific capacity by requesting methodological alternatives and inhibiting the role of researchers in the recruitment of vulnerable people in the country.

In December 2000, an article in the US *Washington Post* newspaper⁴⁰ denounced the diversion of research projects from core countries to countries in Eastern Europe, BRICS and Latin America, aiming at easier recruitment with less structured ethical rules. That article generated an editorial in *Folha de S. Paulo* newspaper⁴¹ disclosing information already known to Conep. In Brazil, a growing number of comparative projects using placebo were being submitted and analyzed, given the well-established evaluation system already in place. Protocols that did not conform to the principles and rules of CNS resolutions were recommended to modify the necessary points, and many others were not approved.

In 2009, a comparative study of the percentages of projects with placebo registered in several countries found that the rate was 12.5% in Brazil and 10.2% in the United States. Such results differ considerably from those of other major international clinical trial sites, such as Mexico (33.8%) and Argentina (39.7%), or Romania (33.9%) and South Africa (33.3%)^{42,43}.

In terms of monitoring projects, in 2001 Conep created the National Information System on Research Ethics (Sisnep), aiming to register research carried out in the entire country. In 2012, Sisnep was replaced by Plataforma Brasil, integrating all CEPs into Conep, an outstanding organizational advance even among core countries.

An enormous growth was observed of the CEP/Conep System, which, together with the analysis of special areas in Conep, approves or rejects proposals. Based on ethical issues found in the projects, this system enabled the debate on the use of placebo and the responsibility to continue treatment after research, creating adequate regulation to protect the people involved, acknowledged by the international community. Thus, it fulfills its role and non-approved projects had to be modified and resubmitted. Resistance has rekindled, mainly from the pharmaceutical industry, through recruited academic researchers and bodies directly representing their trade interests, such as the Representative Organization for Clinical Research, which persistently put forward new proposals to counter this system, based on operational difficulties.

The internal issues of the CEP/Conep System are still a great challenge, as elsewhere in the world. In addition to the difficulties to ethically monitor ongoing research, try to bring Conep closer to the CEPs and other research partners and comply with analysis terms, there was discontent in the field of human and social sciences, which felt left out of CNS. This required a new review to recognize that knowledge of human and social sciences is generated in intersubjectivity, as researchers and their interlocutors are active actors in the research process⁴⁴.

Thus, after extensive discussion in society, CNS Resolution 196/1996²⁷ is reviewed and amended by CNS Resolution 466/2012⁴⁵, without major changes but incorporating some

aspects such as the need for a more complex informed consent process than the informed consent form and an explicit consent form for minors and incapable persons. The document also introduces the term “research participant” in place of “research subject” and makes clear the guaranteed access to medication after the study and the unethical use of placebo when there is a proven prophylactic, diagnostic or therapeutic method.

These were points previously defended by Conep, approved by CNS and taken by the Brazilian Medical Association to the 2008 World Medical Association meeting in Seoul, South Korea, when Brazil defended the proposal to maintain the text of the *Declaration of Helsinki*¹⁰ of 2000, proposing the exclusion of the 2008 text that expanded the possibility of using placebo. Despite support from the United Kingdom, South Africa, Uruguay, Portugal and Spain, the proposal from the United States prevailed, allowing the use of placebo in new situations^{46,47}.

From the viewpoint of the ethical evaluation flowchart, CNS Resolution 466/2012⁴⁵ simplifies the analysis of multicenter projects, which are now presented only by the coordinating center, thus speeding up the process. However, this resolution did not address human and social sciences, which led the CNS to enact CNS Resolution 510/2016⁴⁸, following mobilization by academic groups in that field. These guidelines changed the relationship between CEPs and researchers in the area, who now take effective part in discussing the system. Hallmarks of this document include registration of consent, which can be done in other ways besides writing, the particularities of analysis in the field and of considerations about research risks, and the definition of criteria for projects that do not require analysis by a committee.

Importance of social control

The international and Brazilian ethical regulations resulted from the questioning and mobilization of society. The word “ethics,” from the Greek “*ethos*,” relates directly to the way of being of the individual who recognizes the value of others²⁴. Besides generating knowledge, research must be an agent of change in society.

Thus, an ethical control system that does not include the maintenance of social control in its framework is failing in its duty.

Since CNS Resolution 1/1988⁵, which provided at least one member from outside the institution on the ethics committee, the key role of the external view of science has been incorporated. CNS Resolution 196/1996²⁷, which established a system that presupposes voluntary and multi-professional work, independent operation, social control and representation of specialists and users, aims to ensure the impartiality of judgment required for its legitimacy in society and the character of public office to carry out its mission.¹⁶ Hence, CEPs are an organized form of social control over scientific practices²⁸.

The first supplementary standard of the system was CNS Resolution 240/1997⁴⁹, which defined user representatives as people capable of expressing points of view and interests of individuals and/or groups of research subjects of a given institution and represented different collective and public interests. It should be noted that the CEP system should constitute a true space for democratic debate and plays an important social role, from which lessons can be extracted to be applied in other fields of public policy¹⁸.

In this context, the lessons learned from the participation of members with legitimate voices from outside the institution, such as health councils, associations of people with a certain health condition, graduate students, etc., are successful in demonstrating the system's gains. Among such benefits are the visibility of the rights of research participants, the demand for the disclosure of research results and the questioning of the burden assumed by extensively studied communities that neither receive the benefits of research nor have their reality changed. Currently, the cooperation of representatives of research participants is regulated by CNS Resolution 647/2020⁵⁰.

Alongside this movement, the participation of researchers in health councils evidences the possibility of seeking to understand the demands of the area outside academia. A good example was the broad participation in the 16th National Health Conference (8th+8)¹. It is important to remember that the scientific milieu is not neutral and that society must be alert to what is done at

the boundaries of science and ethics to ensure the uncompromising defense of respect for human dignity⁵¹.

Critical analysis of the current system

The CEP/Conep System has evolved over time and new generations of researchers have been educated with a different perspective on ethical care and the submission of projects to ethical evaluation. More than that, there is a concern with the return of research results to society, even more so because people started following the discussions more closely.

Freitas reports that, *from January 1997, when CEP registrations first started, to February 1998, 161 institutions applied for registration (...) [and] 122 were approved, [and these] belonged to the major research institutions in Brazil, naturally following its geographic distribution*⁵², with prevalence in the states of the Southeast Region followed by the South Region. In the CEP map for October 2021, made available by Conep, 863 committees are registered, with the highest concentration still in the Southeast Region but now followed by the Northeast Region⁵³.

According to Binsfeld⁵⁴, based on 2019 data, the CEP/Conep System comprises approximately 14,000 CEP members and 35 Conep members, and is expanding in several aspects, such as: 1) number and complexity of research projects, with almost 100 thousand projects per year in different areas of knowledge; 2) number of national and international researchers, with more than 110 thousand new researchers registered on Plataforma Brasil in 2018; 3) number of CEPs, with 60 new CEPs created per year on average over the last three years; 4) number of biobanks—by late 2018, around 90 biobanks were registered with Conep; and 5) number of research participants, with close to 2.5 million per year.

However, there are still many asymmetries between the committees, which impacts the processing time of projects with participating and/or co-participating centers in several Brazilian states, requiring an expanded qualification policy. Some problems observed in the system are related to members with inadequate training to deal with the complexity of ethical dilemmas and

scientific methodologies, coordinators elected by undemocratic means and poor attention given to user representatives. Added to that are operational problems of Brazil Platform, which is insufficiently user-friendly and overly bureaucratic, preventing the smooth monitoring of projects by users and the public.

Some actors are critical of the time required to evaluate projects, which encourages the processing of Bill 7,082/2017⁶, which aims to review the process of ethical analysis of clinical research. It proposes a national agency linked to the Ministry of Health, with merely normative, administrative and appeal functions, and another local agency, which would decide on the submitted protocol within 30 days. This is justified by the legal uncertainty of Brazilian regulation, the need for an agile clinical protocol authorization system capable of attracting international investors and the demand for a framework similar to the global regulatory scene.

However, in 2019, the processing time at Conep was within regulations, that is, this factor no longer supports the Bill⁵⁴. However, it is known that this legislation includes other interests, intending to align Brazilian regulation with the current version of the 2013 Declaration of Helsinki¹⁰, of which Brazil is not a signatory for disagreeing with the use of placebos and the limited access to post-study medication. It is important to stress that the Brazilian position is an example of the struggle for equity, justice, non-discrimination and respect for the rights of participants⁵⁵.

It is fitting to mention previous experiences, as there has been pressure since the implementation of the system, which has been protected by the support of academic groups and institutions of scholars and researchers, in addition to civil society. In 2007, correspondence from *Grupo de Incentivo à Vida* (Life Incentive Group)⁵⁶ against HIV/AIDS clearly describes the follow-up of the MK-028 research project with the drug that would later become Indinavir. The then president and secretary of the group, signatories of the correspondence, report that *unlike the CEPs of some hospitals, [Conep] requested opinions from independent consultants, and further down witnessed the enormous pressure suffered by Conep, especially from the trials coordinated from abroad, concluding with the request that AIDS projects continue to be analyzed by Conep*⁵⁶. The project had received an opinion from

Conep to include in the control group the therapy recommended in the Brazilian protocol for the treatment of AIDS, even though it had been approved by the CEP without said recommendation⁵⁷.

The system has achieved prominent goals, even though there is still much to be developed in view of the pressing needs to improve the ethical quality of protocols, especially of what is called “clinical research,” which involves the ultimate application of science in practical medicine, that is, the testing of new drugs, an area that involves important commercial interests. Several authors claim that there is sufficient evidence in the international literature that countless people in the world take part in ethically deficient clinical research^{37,58-60}. Many of those research projects are carried out because they have not been sufficiently challenged from a scientific and ethical point of view, including with regard to their social value^{37,58-60}.

Some international evaluations show the need for special qualification to analyze clinical research projects for new drugs, which are complex in methodology and sometimes lack transparency regarding their possible conclusions. These characteristics require well-established expertise from the members of committees or commissions, suggesting specific training of groups in charge of this kind of analysis⁵⁸. This factor could be considered to improve the efficiency of the Brazilian system, especially with the available structure and role of Conep.

The United Kingdom and Germany also have a central committee that evaluates clinical trials, and these are countries that are acknowledged to actively protect participants. Aware of the situation in Latin American countries, Ugalde and Homedes^{37,59-60} call attention to the fact that regulations differ from one country to another and governments change them frequently. The changes do not always result in stricter standards that incorporate more recent ethical debates or reviews from recognized international institutions. Sometimes they take one step forward, at others they take two steps back. The authors cite the case of Argentina, with Provision 6,677/2010 of *Administración Nacional de Medicamentos, Alimentos y Tecnología Médica*, and of Peru, with Supreme Decree 6/2007, which reversed previous regulations^{37,59,60}.

Research of new products involving humans can bring immeasurable benefits to medical diagnosis

and treatment and should not be hindered by daunting regulation, especially if bureaucratized, a trend that has marked standards and procedures. On the other hand, an increasing number of victims of ethically unthinkable research practices have been identified, whose protection depends on qualified regulatory systems, prepared to deliberate in a democratic and respectful way, equally accessible to experts and laypersons, and ready to be accountable to the society that created them. The number of beneficiaries of the CEP/Conep System to date should be calculated, including those who were not involved in inadequate research forbidden by the system.

Challenges in times of pandemic

The year 2020 was marked by the worldwide havoc wrought by Sars-CoV-2, generating mobilization largely led by the World Health Organization in search of surveillance, care and research strategies. The US government website ClinicalTrials.gov⁶¹ recorded 4,483 studies on COVID-19 as of January 16, 2021, and 7,220 as of December 31, 2021. In Brazil, data from the National Health Surveillance Agency⁶² showed registration of 60 and 121 clinical trials, respectively, at the beginning and end of 2021, and Conep⁶³ approved, from February 17, 2020, to December 4, 2021, 358 interventional/experimental protocols related to coronavirus and/or COVID-19. This scenario posed challenges to CEPs related to the delivery of speedy analysis without loss of evaluation quality and to a differentiated view of the rights of research participants, many of whom were included in protocols with the consent of legal representatives, being as they were in an unconscious state in intensive care units.

Bramstedt⁶⁴ reports that given the accelerated pace imposed by the pandemic on research institutions and, consequently, CEPs, it is worth reflecting on possible flaws in the evaluations, since not all committees were expected have immunologists, microbiologists and pulmonologists as regular members, although they are essential in the analysis of research protocols on this subject. It also emphasizes that CEPs could resort to consultants for these assessments⁶⁴. On the other hand, data point to important methodological

flaws in trials submitted during this period, such as inadequate primary outcomes, small sample size, studies without an adequate control group and sampling excluding important age groups regarding priority to receive the vaccine against COVID-19^{65,66}.

Novaes and collaborators⁶⁷ showed that Conep acted quickly to guide CEPs and researchers in conducting studies on this subject by means of special reports and bulletins. However, Conep's current publications do not clarify data from COVID-19 projects that were not approved in this period nor the ethical reasons for their rejection. Thus, given the pressure coming from different sectors of society and fundamental political issues, maintaining centralized social control proves to be important to ensure the autonomy of the review process as well as maximum possible independence from private interests, preserving structural capacity for the adequate protection of the rights of research participants and for the analysis of the social relevance of projects.

Final considerations

Thirty-four years after the enactment of CNS Resolution 1/1988⁵, the social control policy called CEP/Conep System is definitely consolidated. This is one of the largest voluntary systems in Brazil, having evaluated 91,944 projects in 2018, with around than 3 thousand of them analyzed by Conep, which succeeded in reducing its analysis time to 25 days⁶⁸. Greater interaction between the various research actors, through events organized by large associations, such as the Brazilian Society of Bioethics, Brazilian Society for the Advancement of Science, Brazilian Community Health Association and Conep itself, favors a fruitful dialogue capable of overcoming the barriers of some entities that proved to distrust the national regulatory system.

The rights of research volunteers have been widely disclosed, with Conep paying close attention to the requests of those who benefit from conducting studies in Brazil. An example is CNS Resolution 563/2017, which *regulates the right of research participants to post-study access [to drugs] in clinical research protocols aimed at patients diagnosed with ultra-rare diseases*⁶⁹.

Internal pressure has also frequently tried to undermine independent evaluation in the CEP/Conep System, either through incidental political forces or through the struggle for power in the Ministry of Health, which would rather have Conep as a subordinate body in its administrative framework. It should also be noted that research entities have pressed and continue pressing for a system that is more conducive to their interests. Conep has only been able to preserve and guarantee its autonomy to date thanks to the awareness of its members of its mission and to the protection afforded by its connection

with CNS, a body with expanded representation among society.

Thus, Fonseca¹⁶ reflects on which path we wish to follow: to support and strengthen a system that effectively seeks to guarantee the rights of participants or to favor the formation of other bodies that are more aligned with global development interests, to the detriment of the bioethical principles that guide science? Why take a step back when we have come so far and the momentum of such widespread participation drives us forward towards growth in scientific and ethical capacity?

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